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PROLONGED USE OF A SULFONAMIDE COMPOUND IN PREVENTION OF RHEUMATIC RECRUDESCENCES IN CHILDREN

AN EVALUATION BASED ON A FOUR YEAR STUDY ON SIXTY-FOUR CHILDREN

ARILD E. HANSEN, M.D.

RALPH V. PLATOU, M.D.

AND

PAUL F. DWAN, M.D.

MINNEAPOLIS

Early attempts by us to use sulfanilamide as a prophylactic agent in rheumatic fever were discontinued because of the fear of provoking toxic manifestations of this then new drug. The encouraging results obtained by Coburn and Moore [1] and Thomas and France,[2] however, prompted us to resume this study. Our special purpose was to follow the course of the disease in a group of patients made up entirely of children wherein the control and the sulfanilamide-treated subjects were as nearly as possible comparable and yet under more or less uncontrolled conditions which closely approximated those encountered in the private practice of medicine. Although a relatively large number of patients were observed by Coburn and Moore,[3] comparatively few children were in the control series; Thomas, France and Reichsman [4] used older subjects

From the Department of Pediatrics, University of Minnesota.

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1. Coburn, A. F., and Moore, L. V.: The Prophylactic Use of Sulfanilamide in Streptococcal Respiratory Infections, with Especial Reference to Rheumatic Fever, J. Clin. Investigation **18**:147-155, 1939.

2. Thomas, C. B., and France, R.: A Preliminary Report of the Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, Bull. Johns Hopkins Hosp. **64**:67-77, 1939.

3. Coburn, A. F., and Moore, L. V.: The Prophylactic Use of Sulfanilamide in Rheumatic Subjects, M. Clin. North America **24**:633-637, 1940.

4. Thomas, C. B.; France, R., and Reichsman, F.: The Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, J. A. M. A. **116**:551-560 (Feb. 15) 1941.

almost entirely. The recent report of Stowell and Button [5] concerning a fatal granulopenia in a patient who was receiving sulfanilamide for the prevention of rheumatic fever again draws our attention to the dangers possible with measures of this type. On the other hand, the extremely high mortality rate and crippling effect together with the pronounced tendency of rheumatic fever to recur seem to justify rather bold therapeutic and experimental procedures in an attempt to control this devastating disease. It is only with a broad experience (probably more than one clinic is able to have) that physicians will be able to define clearly the indications and limitations of sulfonamide compounds in rheumatic fever prophylaxis.

During the past four years in the cardiac disease clinic of the outpatient pediatric dispensary of the University of Minnesota Hospitals, a total experience of 124 season-cases with 64 different children has been obtained. Subjects ranging from 3 to 16 years were examined, first at weekly and later at one to six week intervals, depending on the severity of the patient's disease and the distance he must travel to come to the clinic for examination. The majority were from families of the lower socioeconomic strata, who, as emphasized by Wilson in her recent publication,[6] are particularly prone to suffer rheumatic recrudescences. Sulfanilamide was given to 53 different patients daily from October into June for a total of 78 season-cases (3 in 1938-1939, 9 in 1939-1940, 20 in 1940-1941 and 46 in 1941-1942). In order that signs of toxicity of the drug would be detected, small doses were given initially, and later 1 to 3 Gm. daily in divided doses was prescribed. During the third season (1940-1941) sulfathiazole was used for 1 patient because sulfanilamide seemed to cause mild gastrointestinal symptoms. Sulfathiazole was given to 2 additional patients during the fourth season (1941-1942). Sulfadiazine was given to several patients for a short time early during the fourth season, but use of this drug was discontinued because of the relatively great expense to the patient. Only 2 patients received sulfanilamide or one of these derivatives for all four seasons, 5 for three seasons, 9 for two seasons and 37 for but one season. The 32 control subjects were of comparable age and sex, had had about the same number of attacks of rheumatic fever and had suffered about the same degree of cardiac involvement. They were observed for a total of 46 season-cases (4 in 1938-1939, 13 in 1939-1940, 21 in 1940-1941 and 8 in 1941-1942). Three served as controls for three seasons, 7 for two seasons and 23 for but one season. At each visit to the dispensary, in addition to the physical examination, a careful history regarding symp-

5. Stowell, D. D., and Button, W. H., Jr.: Observations on Prophylactic Use of Sulfanilamide on Rheumatic Patients with Report of One Death, J. A. M. A. **117**:2164-2166 (Dec. 20) 1941.

6. Wilson, M. G.: Rheumatic Fever, New York, Commonwealth Fund, Division of Publications, 1940.

TABLE 1.—*Summary Data on 25 Children Not Given Sulfonamide Compounds for the Prevention of Rheumatic Recrudescences Observed During the Three Seasons 1938-1939, 1939-1940 and 1940-1941 for a Total of 38 Season-Cases*

Miscellaneous Data						Anatomic Diagnosis *						Comment	
						Valvular Disease		Size of Heart		Functional Classification *			
Case No.	Age, Yr.	Sex	Age at Onset, Yr.	Heart Disease at Yr.	R. F. Episodes, No.	Intital	Present	Initial	Present	Initial	Present	Infections of Respiratory Tract, No.	Types of Recrudescences
1	7	♀	7	9	1	?	MI	N	N	I	I	1	Hemichorea 1939-1940; chorea 1940-1941
2	11	♂	11	11¼	1	MI	?	N	N	I	I	4	No recurrence 1938-1939; 1939-1940; 1940-1941
3	8	♂	7½	7½	1	AI-MI	AI-MS and MI	+++	+++	IV	III	6	Moderately severe recurrence 1938-1939; no recurrence 1939-1940
4	12	♂	12	12	1	0	0	N	N	Pot.	Pot.	0	Mild recurrence 1939-1940; no recurrence 1940-1941
5	5½	♂	2	5¾	2	MI	MI	+	+	I	I	3	Mild chorea 1939-1940; mild pains in joints 1940-1941
6	9	♂	2	x	4	0	?	N	N	Poss. and pot.	I	1	No recurrence 1940-1941
7	11	♂	10½	11	2	?	?	N	N	Poss. and pot.	Poss. and pot.	1	Repeated pains in joints 1940-1941
8	8	♀	3	8	4	MI	MI	+	++	I	II	1	Moderately severe recurrence 1940-1941
9	12	♀	12	12¼	1	MI	MI	+	++	I	I	0	No recurrence 1940-1941
10	14	♀	11	11	2	MI	MI	++	++	II	II	0	Mild recurrence 1940-1941
11	13	♀	13	13	1	MI	MI	+	N	I	I	0	No recurrence 1940-1941
12	11	♀	11	11	5	MI	MI	N	N	I	I	5	Mild chorea 1940-1941
13	7	♀	7	7	1	MI	MI	+++	+++	IV	III	4	No recurrence 1938-1939; moderately severe recurrence 1939-1940; no recurrence 1940-1941
14	7	♂	7	7½	1	MI	MI	N	N	I	I	1	No recurrence 1940-1941
15	14	♂	12	12½	3	AI	AI	+	+	I	I	..	No recurrence 1940-1941
16	15	♂	10	12	5	MI and ? AI	MI	N	N	I	I	1	No recurrence 1940-1941
17	13	♀	9	9¼	3	MI	MI	++	++	II	II	1	Moderately severe recurrence 1939-1940
18	13	♀	9	9¼	2	MI	MI	++	++	III	II	1	Mild recurrence 1939-1940; moderately severe recurrence 1940-1941
19	11	♀	11	11	1	?	?	N	N	Poss. and pot.	Poss. and pot.	1	Mild chorea 1939-1940
20	15	♀	15	15⅙	1	MI	MI	+	+	II	I	1	No recurrence 1938-1939; no recurrence 1939-1940
21	11	♀	8	?	2	?	MI	N	N	Poss. and pot.	I	2	Moderately severe recurrence 1939-1940; mild recurrence 1940-1941
22	12	♀	8	12	1	MI	MI	N	N	I	I	1	No recurrence 1940-1941
23	14	♂	10	10	2	MI	MI	N	N	I	I	2	No recurrence 1939-1940; no recurrence 1940-1941
24	13	♂	12¼	13	2	MI	MI	N	N	I	I	2	Mild chorea; pains in joints 1939-1940; mild recurrence 1940-1941
25	7	♀	7	7⅙	1	MI	?	N	N	I	I	3	Moderately severe recurrence 1940-1941

* These are according to the recommendation of the American Heart Association.

TABLE 2.—*Summary Data on 20 Children Given Sulfanilamide for the Prevention of Rheumatic Recrudescences Observed During the Three Seasons 1938-1939, 1939-1940 and 1940-1941 for a Total of 32 Season-Cases*

Miscellaneous Data						Anatomic Diagnosis *						Sulfanilamide			Comment	
						Valvular Disease		Size of Heart		Functional Classification *			Blood Level, Mg. per 100 Cc.			
Case No.	Age, Yr.	Sex	Age at Onset, Yr.	Heart Disease at Yr.	R. F. Episodes, No.	Initial	Present	Initial	Present	Initial	Present	Average Daily Dose, Gm.	Minimum	Maximum	Respiratory Infection, No.	Types of Recrudescence
26	13	♂	7	7½	3	MS-I	MS-I	+++	++	IV	II	1.6	0.9	2.1	2	No recurrence 1940-1941
27*	16	♂	13	14	2	MI	MI	N	N	II	I	2.0	Trace	1.3	?	No recurrence 1940-1941
28 1st yr.	6	♂	2½	3	3	AI-MI	MS-MI	+++	++	IV	III	2.0	0.4	4.3	0	No recurrence 1939-1940
2d yr.	..	..	..	..	..	MI-S	MI	++	++	III	II-I	1.3	0.6	3.9	2	No recurrence 1940-1941
29 1st yr.	12	♂	10½	11¾	2	MI	MI	+	N	III	I	3.0	1.0	3.3	0	No recurrence 1938-1939
2d yr.	..	..	..	..	..	MI	MI	+	N	I	I	3.0	Trace	3.3	0	No recurrence 1939-1940
3d yr.	..	..	..	..	..	? MI	MI	N	N	I	I	2.0	Trace	2.4	0	No recurrence 1940-1941
30 1st yr.	15	♂	15	15	1	MS-I	MS-I	+++	++	IV	II	1.3	1.5	3.5	1	No recurrence 1939-1940
2d yr.	..	..	..	..	..	MS-I	MS-I	++	+	II	I	1.6	1.2	2.4	1	No recurrence 1940-1941
17	16	♂	9	9	4	MS-I	MS-I	+	N	II	I	1.5†	3.1†	3.6†	0	No recurrence 1940-1941
16	16	♂	10	12	4	MI-AI	MI-AI	N	N	II	I	2.0	1.7	3.8	1	No recurrence 1939-1940
31	16	♂	15	15	1	? MS-I	MI	+	N	II	I	2.0	0.9	3.6	3	No recurrence 1940-1941
32	16	♂	13	14	3	MS-I	MS-I	++	N	II	II	2.0	2.8	4.2	3	No recurrence 1940-1941
33	10	♂	8	8½	1	MS-I	MS-I	+++	+++	III	II	1.3	2.1	7.6	0	Possible mild recurrence 1940-1941
34	15	♂	9	9¼	4	MS-I-AI	MS-I-AI	+++	++	IV	II	2.0	3.6	7.8	0	No recurrence 1940-1941
3	8	♂	7½	7½	3	MI-AI	MI-AI	+++	++	IV	II	2.0	2.3	3.4	2	No recurrence 1940-1941
35 1st yr.	5½	♀	5	5½	1	MI	MI	++	++	IV	I	1.0	1.5	5.3	3	No recurrence 1939-1940
2d yr.	..	..	..	..	..	MI	MI	++	++	I	I	2.0	4.7	7.2	2	No recurrence 1940-1941
19	12	♀	11	11⅛	1	0	0	N	N	Potential	Potential	1.3	0.6	1.5	3	No recurrence 1940-1941
36 1st yr.	11	♂	9	9⅛	2	MI	MI	+	+	I	I	3.0	Trace	5.4	1	No recurrence 1938-1939
2d yr.	..	..	..	..	..	MI	MI	+	+	I	I	3.0	Trace	4.0	0	No recurrence 1939-1940
3d yr.	..	..	..	..	..	MI	MI	+	+	I	I	1.3	Trace	2.8	1	No recurrence 1940-1941
37 1st yr.	4	♂	4	4⅛	1	MI-AI	MI-AI	+++	++	II	I	1.3	2.1	4.5	2	No recurrence 1939-1940
2d yr.	..	..	..	..	..	MI-AI	MI-AI	++	++	I	I	1.3	Trace	4.1	2	No recurrence 1940-1941
38 1st yr.	10	♂	6	6 1/10	4	MI-MI	MI-MI	++	++	II	II	2.0	1.5	5.3	1	No recurrence 1939-1940
2d yr.	..	..	..	..	..	MI-MI	MI-MI	++	++	II	I	1.3	1.8	5.1	0	No recurrence 1940-1941
39 1st yr.	10	♂	8	10	2	MI-MI	MI-MI	++	++	II	I	1.3	Trace	1.1	0	No recurrence 1939-1940
2d yr.	..	..	..	..	..	MI-MI	MI-MI	+	+	I	I	1.3	Trace	2.8	0	No recurrence 1940-1941
40	10	♀	10	10	2	MI	MI	N	N	II	I	2.0	1.1	5.3	2	No recurrence 1940-1941
41	15	♂	15	15¼	1	MI	MI	++	+	I	I	2.0	Not taken	...	0	No recurrence 1938-1939; no recurrence 1939-1940

* These are according to the recommendation of the American Heart Association.
† Sulfathiazole was used.

toms which may have been of rheumatic origin as well as the occurrence of infections of the upper respiratory tract was elicited. Determinations of the hemoglobin, leukocytes, differential white cell count and sedimentation rate of the red blood cells and recently cultures of material from the throat were obtained. For the patients receiving a sulfonamide compound the levels of the drug in the blood were determined. At intervals of three to six months electrocardiographic tracings and roentgenograms of the heart were made.

In this report detailed information is presented for the patients studied during the first three years (1938-1939, 1939-1940 and 1940-1941). Pertinent data regarding age, sex, age at onset, previous rheumatic episodes, diagnosis, functional classification, infections of the upper respiratory tract and rheumatic recrudescences for the 25 control subjects and the 20 patients who were given a sulfonamide compound for the first three seasons are summarized in tables 1 and 2 respectively.

In table 3 the electrocardiographic findings, including the rate, PR intervals and axis at the beginning and at the end of the period of observation, are given for the subjects studied for the first three years, as well as a summarizing statement regarding the changes which were observed after the individual tracings for all the patients were studied.

In addition, findings regarding the incidence of rheumatic recurrences for the 54 patients (46 treated with a sulfonamide compound and 8 control subjects) who were studied during the fourth season (1941-1942) are presented in the summary table (table 4).

OBSERVATIONS

Frequency and Type of Recurrence.—Of the 25 control subjects studied for the first three seasons (table 1), only 10 patients escaped with no recurrence; the other 15 experienced a total of 19 rheumatic episodes. In 7 patients the attacks were moderately severe; in another 7 they were mild, and in 5 chorea occurred. In striking contrast to these results, only 1 child in the group of 20 patients receiving a sulfonamide compound during the same seasons experienced mild rheumatic symptoms.

During the fourth season (1941-1942) only 8 patients served as control subjects, and of these 1 experienced a moderately severe recurrence and 1 other a mild but prolonged active rheumatic cycle. Forty-six patients were given a sulfonamide compound, but 2 discontinued using the drug when the season was about half over. One child in this treated group acquired typical polyarthritis with fever, but the onset of this attack was only six days after the use of the drug was instituted. It now seems to be well established that the use of a sulfonamide compound does not prevent the development of rheumatic recrudescences within a period of two weeks after the first administration of the drug. In the case of another subject all seemed to be going well when sulfa-

TABLE 3.—*Summary of Electrocardiographic Findings in Patients Studied During the First Three Seasons (1938-1939, 1939-1940, 1940-1941)*

Case No.	Rate		PR Interval		Axis		Comment: Changes Observed Throughout the Period of Study
	Initial	Present	Initial	Present	Initial	Present	
							A. Control Subjects
1	120	88	0.14	0.16	+76°	+77°	No signs of myocardial damage except frequent auricular extrasystoles, probably of no significance (1939-1940; 1940-1941)
2	88	66	0.16	0.16	+55°	+41°	Normal throughout (1938-1939, 1939-1940, 1940-1941)
3	60	76	0.24	0.21	+60°	+50°	Irregular, large P waves; persistent first degree block; (PR 0.20-0.25, 1938-1939). Conduction time returned to normal with notching of P waves (1939-1940)
4	94	76	0.12	0.14	+42°	+55°	Normal tracing throughout (1939-1940; 1940-1941)
5	90	92	0.15	0.14	+ 5°	0°	Tendency to left axis deviation (1939-1940). No definite changes (1940-1941)
6	84	81	0.20	0.16	+65°	+53°	No early tracings available; changing axis and fluctuations in ST intervals suggest possibility of some myocarditis; rapid return of conduction time to normal (1940-1941)
7	100	90	0.15	0.17	+65°	+65°	Persistent, though slight, changes in contour of P waves; significance of these questionable (1940-1941)
8	118	77	0.18	0.16	+78°	+67°	Tracings within normal limits but for mild tachycardia early in year; tendency to right axis deviation (1940-1941)
9	102	80	0.17	0.15	+72°	+65°	Within normal limits throughout (1940-1941)
10	84	96	0.19	0.20	+65°	+45°	Persistent prolongation of PR interval; large, irregular P waves; prominent Q_3; no significant new changes (1940-1941)
11	70	65	0.20	0.17	+70°	+53°	Within normal limits (1940-1941)
12	115	80	0.16	0.15	+72°	+50°	Within normal limits during entire year (1940-1941)
13	130	83	0.16	0.17	+65°	+60°	Pronounced improvement from earlier tracings; slurring of QRS_1 and irregular, deformed P waves a constant feature (1938-1939). No significant changes (1939-1940; 1940-1941)
14	88	90	0.18	0.19	+74°	+85°	Irregular diphasic and notched P waves throughout (1940-1941)
15	100	110	0.20	0.21	+55°	+55°	Prolonged conduction time and changing contour of P and T waves suggest continuous myocardial changes; axis shifted toward left with development of clinical evidences of an aortic lesion (1940-1941)
16	107	54	0.16	0.15	+67°	+45°	Alterations in contour of P waves; persistent tachycardia; delayed AV conduction early in year (1939-1940). Little change (1940-1941)
17	134	110	0.19	0.17	+80°	+50°	Remarkable changes in tracings; tachycardia decreased only slightly; Swift leads disappeared; voltage improved; P waves regained a fairly normal contour; axis shifted progressively (1939-1940)
18	110	90	0.18	0.15	+69°	+60°	Tachycardia, prolonged PR interval and Swift leads disappeared early in year, leaving P waves as only abnormal finding (1939-1940). No significant change; P waves remained large but conduction time normal (1940-1941)
19	115	84	0.16	0.18	+61°	+46°	Tracings normal but for sinus tachycardia during first admission; some alterations in contour of T waves (1939-1940)
20	70	110	0.20	0.14	+70°	+55°	Within normal limits but for slurred QRS and slight irregularity in contour of P waves (1938-1939; 1939-1940)
21	70	90	0.19	0.18	+81°	+85°	Changes more pronounced early in year; later improved with return of conduction time to normal (0.16-0.18) (1939-1940; 1940-1941)
22	114	82	0.17	0.14	+68°	+55°	Tracings within normal limits but for slight irregularity of P waves (1940-1941)
23	76	106	0.18	0.21	+90°	+68°	Numerous Swift leads early in year; cleared with return of conduction time to normal; slurring of QRS complexes remained a constant feature (1939-1940). Slurring of QRS became more pronounced; P waves more irregular and larger; conduction time always at upper limits (1940-1941)
24	58	80	0.26	0.19	+56°	+60°	PR interval prolonged (0.23-0.26) early in year, with second degree block but no other abnormal changes (1939-1940). No change but for continuance of AV conduction at upper limits of normal (1940-1941)
25	115	87	0.14	0.16	+80°	+75°	Tracings normal (1940-1941)

B. Patients Receiving Sulfanilamide Prophylactically

26	150	64	0.21	0.16	+72°	+77°	Remarkable improvement (1940-1941)
27	88	90	0.21	0.22	+70°	+60°	Persistent delayed AV conduction (0.20-0.23) with increasing deformity of P waves (1940-1941)
28 1st yr.	136	102	0.14	0.15	+62°	+62°	Pronounced improvement from earlier tracings; normal (1939-1940)
2d yr.	102	90	0.15	0.15	+68°	+68°	Unchanged but for increasing deformity of P waves (1940-1941)
29 1st yr.	90	78	0.20	0.16	+60°	+55°	Normal except slightly irregular P waves, negative in lead III (1938-1939)
2d yr.	78	60	0.16	0.15	+55°	+55°	Slightly increased slurring of QRS (1939-1940)
3d yr.	60	60	0.15	0.15	+60°	+55°	No change (1940-1941)
30 1st yr.	130	114	0.24	0.18	+34°	+ 6°	Pronounced improvement over earlier tracing (1939-1940)
2d yr.	114	94	0.18	0.18	+36°	+ 8°	Low voltage in lead III; persistent left axis deviation; conduction time returned to normal; P waves slightly deformed (1940-1941)
17	102	110	0.19	0.17	+65°	+75°	No significant change except occasional Swift leads; slight increase in width of P waves (1940-1941)
16*	125	82	0.18	0.16	+67°	+65°	Only one tracing available; rate slower, block persisting (1939-1940). No change (1940-1941)
31	75	80	0.16	0.16	+50°	+58°	Increasing deformity (notching) of P waves; moderate sinus tachycardia (1940-1941)
32	110	82	0.20	0.20	+35°	+40°	Slightly prolonged AV conduction with alterations in contour of P waves, no acute changes during this period, 1940-1941
33	82	84	0.17	0.14	+98°	+100°	Persistent right ventricular strain, frequent changes in size and contour of T waves, variable conduction time (these changes suggest continuous myocardial activity) 1940-1941
34	125	80	0.18	0.17	+30°	+45°	Large, irregular P waves throughout; conduction time returned to normal (1940-1941)
3	80	76	0.22	0.21	+67°	+50°	No significant changes (1940-1941)
35 1st yr.	88	80	0.21	0.17	+111°	+86°	Large, irregular, notched P waves; early delayed AV conduction with digitalization; persistent right axis deviation (1939-1940)
2d yr.	82	80	0.18	0.20	+86°	+86°	Rate slowed progressively; sinus arrhythmia reappeared; deformity of P waves more pronounced; right axis deviation continued while AV conduction time decreased when digitalization was discontinued (1940-1941)
19	115	80	0.16	0.19	+61°	+117°	Prolonged AV coduction early, with return to normal during year (1940-1941)
36 1st yr.	120	80	0.24	0.19	+65°	+55°	Persistent first degree block (PR 0.24-0.25) with deformed P waves; tachycardia, early (1938-1939)
2d yr.	90	76	0.25	0.20	+74°	+72°	Conduction time improved (0.19-0.20); slight slurring of QRS complexes (1939-1940)
3d yr.	76	65	0.20	0.19	+72°	+55°	No significant change from past year (1940-1941)
37 1st yr.	112	90	0.16	0.14	+70°	+55°	Tachycardia, with tendency to right axis deviation (1939-1940)
2d yr.	90	100	0.14	0.14	+55°	+83°	Slower rate; axis shifting back to normal range; noticeable deformity of P waves (1940-1941)
38 1st yr.	105	74	0.21	0.16	+76°	+73°	Sinus tachycardia; Swift leads present during early part of year; normal tracings within three months (1939-1940)
2d yr.	76	74	0.17	0.15	+64°	+73°	Tracings remained within normal limits (1940-1941)
39 1st yr.	72	94	0.16	0.14	+65°	+65°	No signs of myocardial damage developed; Ts persistently isolectric or negative (1939-1940)
2d yr.	94	..	0.15	....	+65°	.....	No significant changes (1940-1941)
40	100	96	0.24	0.20	+60°	+57°	Persistent first degree heart block (PR 0.20-0.22); sinus tachycardia at times (1940-1941)
41	76	..	0.14	....	+15°	.....	Within normal limits (1938-1939). No change (1939-1940)

* Sulfathiazole was used.

diazine was used, but because of the expense involved sulfathiazole was substituted. About six weeks later a leukopenia developed; so the use of the drug was stopped in February 1942. Two small transfusions were given as a precautionary measure, and the leukocyte count soon rose. No recurrence of rheumatic fever developed during the next three months. In June 1942 this girl, now 17 years old, had a sudden severe illness with high fever and was admitted to the Medical Service of the University Hospital. Streptococcus viridans was isolated from the blood on repeated cultures during the next two weeks. Sulfadiazine

TABLE 4.—*Summary of Cases by Seasons*

Control Subjects			Sulfonamide-Treated Subjects	
No.	Comment		No.	Comment
		1938-1939		
4	1 moderately severe recrudescence		3	No recrudescences
		1939-1940		
13	8 recrudescences 2, mild chorea 1, hemichorea 2, mild symptoms 3, moderately severe		9	No recrudescences
		1940-1941		
21	10 recrudescences 2, chorea 5, mild symptoms 3, moderately severe		20	1 mild recrudescence
		1941-1942		
8	2 recrudescences 1, mild chorea 1, moderately severe		46*	1† moderately severe recrudescence
		Total Season—Cases		
46	21 recrudescences 6, chorea 7, mild symptoms 8, moderately severe symptoms		78	2 recrudescences 1 moderately severe recrudescence †

* Three patients did not continue use of the drug throughout the season; in one leukopenia developed, in another polyarthritis occurred and the third moved out of the state.

† Polyarthritis developed six days after use of the drug was instituted.

was administered and caused no essential change in the condition of the patient, and a leukopenia did not develop. She was discharged from the hospital about one month later in poor condition. As noted in table 4, only 2 rheumatic recurrences were observed to occur in the 78 season-cases in which a sulfonamide compound was given, whereas 21 recrudescences occurred in the 46 season-cases in the control group.

Degree of Cardiac Involvement, Size of the Heart and Functional Classification.—When these features as noted at the end of the period of study were compared with those at the beginning during the first three seasons, the following observations were made: The degree of cardiac involvement in the control group (table 1) was interpreted as being

greater in 3 instances, about the same in 21 and less in 1, while the size of the heart was greater in 1, the same in 23 and smaller in 1 subject. In contrast to this, in the cases in which a sulfonamide compound was given (table 2) the degree of cardiac involvement was found to be greater in none, the same in 14 and less in 6, while the size of the heart was greater in none, about the same in 7 and smaller in 13. The same favorable trends were noted in regard to the functional classification: In 8 cases in the control group the functional status was classified as being more severe, in 18 the same and in 4 more favorable, whereas in the cases in which a sulfonamide compound was used the status as regards function was more severe in none, the same in 4 and more favorable in 16.

Gain in Weight, Infections of the Upper Respiratory Tract and General Clinical Observations.—In plotting the curves of the increase in weight made by the various members of each group, no essential differences could be detected; so it seemed that the administration of sulfanilamide did not impair normal increase in weight. From the data collected concerning the incidence of infections of the upper respiratory tract, no essential difference was found between the two groups (tables 1 and 2). On the whole, the clinicians examining these patients were impressed with the general appearance of well-being in most of the sulfanilamide-treated patients.

Hemoglobin, Leukocytes, Polymorphonuclear Leukocytes and Erythrocyte Sedimentation Rate.—In none of the patients who were observed during the first three seasons (table 1) did a severe anemia develop. A hemoglobin level of less than 70 per cent was observed 3 times in patients who were given sulfanilamide, and this was the same incidence as in the control group. Leukocyte counts of less than 4,000 were observed with equal frequency in the two groups, and in no instance was the low white cell count persistent in the patients treated with a sulfonamide compound. The polymorphonuclear cell count was below 38 per cent on 7 occasions in the treated group, while in the control series, with almost as many observations, it was below this level in 3 instances. During the fourth season (1941-1942), however, the use of sulfathiazole was discontinued for 1 patient, as mentioned previously, because the white cell count dropped to 1,700 with 12 per cent polymorphonuclears; the hemoglobin content did not drop in this patient and she experienced no untoward symptoms. A graph of the sedimentation rates of the erythrocytes showed the general trends to be lower and the periods of accelerated rate to be fewer in the sulfanilamide-treated patients.

Dosage, Blood Levels and Toxicity.—Relatively larger amounts of sulfanilamide were given during the first two years (2 to 3 Gm. daily),

and the levels of the drug in the blood tended to be correspondingly higher (table 2). The favorable effect in preventing rheumatic recrudescences seemed to bear no relation to the amount of sulfanilamide given when it was within the limits used. Patients given 1.3 Gm. (20 grains) seemed to fare as well as those given the larger amounts. Our practice recently has been to administer 0.67 Gm. (10 grains) with the morning and with the evening meal. In only 4 instances were rashes discerned, and these were evanescent. In 5 instances mild anorexia or gastric distress was encountered, but these symptoms disappeared when use of the drug was stopped for a few days and then resumed with smaller doses. In 3 instances sulfanilamide was not tolerated, but when it was replaced by sulfathiazole for 2 of the patients and by sulfadiazine for the other no difficulty was encountered. It is well known that the sulfonamide compounds now available are not effective against acute rheumatic fever and actually may cause the symptoms to flare up. On one occasion a rheumatic recrudescence began the day after the administration of sulfanilamide was instituted. The patient, a boy, was found to have fever and articular pains as well as leukocytosis and elevation of the sedimentation rate after having had but two doses of sulfanilamide. It is reasonable that a sulfonamide compound would not prevent an attack which began as soon as this one developed; however, whether or not the drug played any part in this recrudescence is problematic.

Electrocardiographic Changes.—In both the treated and the untreated group there were all degrees of variation in electrocardiographic changes. Some persons in each group showed no abnormal changes whatsoever; others in each group showed changes suggesting continuous activity of the infection in the myocardium. In several cases the changes in the tracings gave evidence of remarkable improvement of the myocardium, but this occurred about as often in the patients who had not been given a sulfonamide compound as in the ones who had been. The number of cases tabulated is too small and the changes altogether too inconsistent to permit any accurate statistical evaluation. However, our findings at least seem to suggest that the sulfonamide compounds used caused no demonstrable myocardial changes even though they were administered for long periods. French [7] has reported that in both human subjects and experimental animals histologic changes in the myocardium are discernible after the administration of various sulfonamide compounds. Our results would indicate that myocardial changes even if present do not cause perceptible changes in the electrocardiograms.

7. French, A. J.: Interstitial Myocarditis in Mice and Rats Produced by Neoprontosil, Sulfanilamide, Sodium Sulfapyridine and Sodium Sulfathiazole, Proc. Soc. Exper. Biol. & Med. **48**:1-3, 1941.

COMMENT

Our experience on the whole has been gratifying. The incidence of 21 rheumatic recrudescences in the control group, comprising 46 season-cases, is a little higher than that usually expected (30 to 35 per cent) [1] but this probably can be explained by two factors: first, the age and social status of the control patients were such as would predispose to recurrence of rheumatic cycles; second, evidence of the beginning of the attacks was carefully sought and the patient placed at complete rest even though the symptoms were mild.

TABLE 5.—*Summary Data Concerning Recrudescences in Patients with Inactive Rheumatic Fever Observed by Various Groups of Workers: Control Patients and Patients Treated with Sulfonamide Compounds*

	Thomas, France and Reichsman Number		Coburn and Moore Number		Stowell and Button Number		Present Series Number	
Ages, Years	Sulfamide	Control	Sulfamide	Control	Sulfamide	Control	Sulfamide	Control
3-13	2	3	184	17	7*	14	53§	32
14-19	29	39		..	..	..	..	..
20-29	15	12	..	129	..	..	..	..
30-37	9	13	..		..	..	..	..
Total season—cases	79	150	188	146	7*	14	78	46
Recurrences	2	21‡	1	31	1	4	2‖	21
Children	2	21‡	1	5	1†	4	2‖	21
Older subjects			..	26	..	..	..	..

	Sulfanilamide-Treated	Control Subjects
Total season-cases (all observers)	352	356
Recurrences (all observers)	6	77

* Forty-six started use of a sulfonamide compound; 16 discontinued its use because of signs of toxicity, mostly cutaneous eruptions; data concerning others not given.

† One death (sudden rise of temperature to 105 F., and agranulocytosis); hemolytic Staphylococcus aureus and Pneumococcus type III cultured from blood stream.

‡ Four deaths, 2 from subacute bacterial endocarditis, 1 from rheumatic fever and 1 from acute fulminating illness.

§ One patient acquired leukopenia (1,700 leukocytes with 12 per cent polymorphonuclears) after taking the drug for five months.

‖ One moderately severe recurrence with polyarthritis developed six days after the drug was first given.

We fully realize that our observations are valuable only when interpreted in the light of and in association with the findings of other investigators on this subject. Accordingly a summary of all information available, including that obtained by Coburn and Moore,[3] Thomas, France and Reichsman,[4] Stowell and Button [5] and ourselves, is presented in table 5.

In the control groups of the various authors mentioned, comprising a total of 356 season-cases, 77 rheumatic recrudescences were observed, and, as may be expected, the proportion of recurrences was greater in

the younger age group. Seven of the major rheumatic episodes in the control series of Thomas, France and Reichsman [4] were in subjects less than 16 years of age. Four deaths, including 2 from subacute bacterial endocarditis, 1 from rheumatic fever and 1 from an acute illness, occurred in their control subjects. It must be emphasized, as stated by Coburn and Moore [8] and Thomas, France and Reichsman,[4] that sulfonamide compounds are effective in preventing rheumatic infections only when the patient is taking the drug and that they do not affect the subsequent course of the disease. In striking contrast to the results in this combined control series, we find that in the patients treated with a sulfonamide compound, with 352 season-cases, but 6 recrudescences were observed. Of particular concern, however, is the death reported by Stowell and Button.[5] It may be that the granulopenia observed in their case was not necessarily due to the sulfanilamide administered. Spink, Hansen and Paine [9] observed an extreme granulopenia in an acutely ill 4 year old child, from whose blood hemolytic Staphylococcus aureus (coagulase positive) was isolated. This child had not been given any of the sulfonamide compounds previously. The leukocyte count on admission was 4,200, with 16 per cent polymorphonuclears, but dropped to 800 in two days, and granulocytes were difficult to find in the blood smear. Sulfapyridine was administered continuously in such amounts that the free sulfapyridine level of the blood ranged from 4.4 to 8.4 mg. per hundred cubic centimeters. During the fourth week of the illness the blood stream became sterile, at which time the leukocyte count rose to 18,250 and then to 24,550, with 68 per cent polymorphonuclears. With this drastic change in the leukocytes a phenomenal change in the clinical condition of the patient occurred. It would appear from this that sulfonamide compounds may be effective against staphylococcic bacteremia, even with profound depression of the granulocytes.

Stowell and Button experienced great difficulty because of the toxic manifestations caused by sulfanilamide in their subjects. Of the 46 patients given the drug in their series, 16 discontinued its use because of signs of toxicity. They did not state how many of their subjects actually suffered rheumatic recrudescences. We have been fortunate in that few of our patients had signs of toxicity. Coburn and Moore [8] found that about 10 per cent of their subjects did not seem to tolerate the drug; however, no serious complications were reported by them. It is hoped that in a relatively short time a more abundant experience

8. Coburn, A. F., and Moore, L. V.: A Follow-Up Report on Rheumatic Subjects Treated with Sulfanilamide, J. A. M. A. **117**:176 (July 19) 1941.

9. Spink, W. W.; Hansen, A. E., and Paine, J. R.: Staphylococcus Bacteremia: Treatment with Sulfapyridine and Sulfathiazole, Arch. Int. Med. **67**:25-35 (Jan.) 1941.

will be available, in order that we may draw more exact conclusions concerning the prophylactic value of sulfonamide compounds in preventing recurrences of the rheumatic cycle. At the present time the findings of the various investigators seem to justify the continued study of this type of therapy, as the evidence is convincing that these drugs are effective in this role. Each patient treated with one of these compounds should be the personal responsibility of the physician, and due precaution should be taken, especially as regards the various blood constituents and urine. The general condition of each particular patient should be known to him at all times.

SUMMARY AND CONCLUSIONS

A sulfonamide compound (sulfanilamide or, in a few instances, sulfathiazole or sulfadiazine) was administered to 53 different children for a total of 78 season-cases to determine their value in preventing the occurrence of active rheumatic cycles, and the results were compared with those observed in 32 control children followed for a total of 46 season-cases. All subjects studied were between 3 and 16 years of age and had had essentially similar histories as regards previous rheumatic episodes, degree of cardiac involvement and social status. These children were observed under conditions which closely approximate those encountered in the private practice of medicine. Only 2 of the 53 children in the group treated with a sulfonamide compound experienced a rheumatic flare-up, and in 1 this occurred within six days after the use of the drug was begun. On the other hand, 17 of the 32 children in the control group had a total of 21 rheumatic recrudescenses. Eight of these recurrences were considered moderately severe; 7 were mild, and in 6 of the subjects attacks of chorea were noted. In addition, the treated patients seemed favorably affected as regards the trend in degree of cardiac involvement, size of the heart and functional classification. No difference was noted in the number of infections of the upper respiratory tract in the two groups, whereas the treated patients gained as well as the patients in the control group and from a clinical viewpoint tended to be in better condition. Toxic manifestations due to the drug and disturbances in blood cells were seldom encountered, although during the fourth season the use of sulfathiazole was discontinued for 1 patient when the number of leukocytes dropped to 1,700. Improvement in electrocardiographic tracings, though suggestive in several instances, could not be attributed to the effects of the drug alone. There was no evidence that the sulfonamide compounds used produced changes in the electrocardiograms which may have been interpreted as being deleterious.

Although this series of cases is relatively small, the results are consistent and when interpreted in the light of the observations of other investigators on this subject appear to justify further study of the practical value of sulfonamide compounds in preventing rheumatic recrudescences. This appears to be especially true when we are aware that this disease is one of the major causes of disability and death in children of school age in the temperate zone. Caution should be the rule, and each child so treated should be under the care of a scrutinizing physician at all times.

1437 East River Road.
Tulane University Medical School, New Orleans.
953 Medical Arts Building.

COCONUT WATER

A CLINICAL AND EXPERIMENTAL STUDY

EMILIO SOTO PRADERA, M.D.

ENRIQUE FERNANDEZ, S.D., PH.D.

AND

OSCAR CALDERIN

HABANA, CUBA

The study on which we are reporting, fostered in the Service of the Chair of Pediatrics, Mercedes Hospital, Havana University, included the following aspects:

1. Biologic value of coconut water, determined through study of its proteins.
2. Importance of the amino acids found in the proteins of coconut water.
3. Relation between the proteins in the endosperm of the coconut and those in the water.
4. Experimental anaphylaxis in the rabbit as a means of determining the presence or absence of sensitizing (complex molecule) proteins in coconut water.
5. Historicobibliographic survey of the medical use of coconut water.
6. Ways of using coconut water in clinical pediatrics, with special reference to feeding of infants.
7. Possibility of parenteral injection of coconut water and the scientific basis for it.

BIOLOGIC VALUE OF COCONUT WATER

In undertaking the study we were motivated by a desire to determine the scientific reasons for the use of coconut water in medical practice, since some of the reasons that had been postulated were rather empiric. We were especially interested in investigating the relation between the proteins in the water of the coconut and those in the endosperm, it having been demonstrated that the water participates in the formation

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Presented before the Pediatrics Convention of Habana.

From the Service of the Chair of Pediatrics, Mercedes Hospital, Havana University.

Dr. Sainz de la Peña, in charge of the Laboratory of Biological Investigation and Pathology of the Chair of Pediatrics, and many others assisted or collaborated in this study.

of the endosperm through a complex mechanism of precipitation. In contrast, however, to the detailed study to which the proteins of the endosperm had been subjected, there seemed to have been no true analytic study of the proteins of coconut water. In a review of current scientific literature we found expressed the percentages of the constituents, namely carbohydrates, lipids, proteins and salts, and for some elements, especially sugars, a more detailed qualitative and quantitative chemical analysis. The protein content was reported as 0.15 to 0.29 per cent (the value for protein nitrogen multiplied by the factor 6.25); but a minute description of the proteins was lacking.

It is not easy to study protein nitrogen so as to determine the type of proteins it integrates. This is especially true in the case of coconut water, in which nature combines and modifies in an acid medium of constant p_H a complex of proteins which are suspended in electrolytes and become partially hydrolyzed in the course of time.

We shall first present the results we obtained with various precipitation tests for proteins and then give the conclusions that may be drawn from them.

Precipitation Tests with Heavy Metals.—Tests with lead acetate, mercuric chloride and zinc sulfate were made with small and with large amounts of coconut water, with negative results.

Precipitation Tests with So-Called Alkaloid Precipitants.—Tests were made with phosphotungstic acid, tungstic acid, phosphomolybdic acid, trinitrophenol (picric acid), metaphosphoric acid and sulfosalicylic acid. Because of the milky precipitate formed by phosphotungstic and phosphomolybdic acids with potassium chloride contained in the water, the results obtained with these two acids were discarded. Results were negative with tungstic acid and trinitrophenol; a slight precipitate was formed in twenty-four hours with metaphosphoric, sulfosalicylic and tannic acids.

Precipitation Tests with Ethyl Alcohol.—Fifty degree alcohol produced no precipitate and 66 degree alcohol only a slight precipitate. Eighty degree alcohol produced a copious precipitate, in which by Kjeldahl's method 17.5 per cent of protein nitrogen was found to be present. After this precipitate was heated, a determination by the same method gave a comparable value (17.0 per cent).

Precipitation Tests with Sodium Hydroxide.—When a sample of coconut water was neutralized with tenth-normal sodium hydroxide, an abundant precipitate was obtained, which increased in a water bath at 60 C. Determination of the nitrogen content of the precipitate by the micro-Kjeldahl method gave a value of 16.5 per cent. When the sample of coconut water was alkalinized by excess tenth-normal sodium hydroxide, the precipitate increased.

None of the other elements of the coconut water (mineral salts, carbohydrates or neutral fats) were found to be susceptible of precipitation by the alkaline solution employed. It was noted that when a previously alkalinized sample of coconut water was heated soaps might be formed with the fatty acids. Though there was only a remote possibility that this would occur in these tests, since nearly all precipitations were effected without heating and, moreover, the fats in coconut water are saturated or neutral fats, nevertheless the fats of the water were separated by means of purified petroleum benzine (petroleum ether) and benzene before the precipitation tests for proteins were made.

Precipitation Test with Dialyzed Ferric Oxide.—There was considerable precipitation. The precipitated proteins were washed with distilled water, alcohol and a combination of ether and alcohol in order to dehydrate them; the process was completed in a crystal desiccator.

Precipitation Test with Cupric Hydroxide.—The results were negative. It should be pointed out that this test is considered important in demonstrating vegetable proteins, the major part being flocculated by this means.

Xanthoprotein Test (Mulder's Test).—Protein solutions treated with nitric acid turn yellow, and yellowish red when the solutions have been alkalinized. With coconut water the reaction to the first part of the test was negative and to the second positive.

Biuret Test.—In this test the problem solution is treated with potassium hydroxide, and a few drops of cupric sulfate solution is then added. If proteins are present, a rose color is obtained, which turns to violet. With coconut water the result was negative.

Millon's Test.—The nitric acid–metallic mercury reagent produces a brick red color with cyclic compounds. Coconut water gave a negative reaction. A faint rose hue was obtained after heating.

Tests for Peptones and Albumoses.—Several such tests were made:

1. Saturated solution of ammonium sulfate produced no precipitate with coconut water. Peptones are not supposed to precipitate with this reagent, but albumoses should.

2. When the sample was treated with potassium sulfocyanate and acetic acid, no precipitate was seen immediately. However, after a few hours a very faint deposit was observed.

3. With trinitrophenol (picric acid) no precipitate was observed immediately but a faint precipitate was demonstrable after twenty-four hours.

4. Trichloroacetic acid yielded no precipitate.

5. Addition of sodium chloride to the sample yielded no precipitate even after boiling.

Tests for Metaproteins.—The sample was alkalinized and the proteins precipitated by means of tenth-normal sodium hydroxide solution; the precipitate contained 16.5 per cent nitrogen, in addition to amino acids (to be studied more fully later). The following tests were then made:

1. Addition of a 0.4 per cent solution of hydrochloric acid to the precipitated proteins made the precipitate disappear. Neutralization with neutral sodium carbonate solution caused it to reappear. This reaction may be considered as positive for metaproteins.

2. When the precipitated proteins were treated with concentrated hydrochloric acid, they redissolved, but they were not flocculated by addition of an excess of this acid. The latter observation does not seem to indicate the presence of metaproteins, as they are known to precipitate in an excess of a strong acid.

3. When the precipitate was dissolved in 0.4 per cent hydrochloric acid and the solution was boiled, no coagulum appeared. After cooling, neutralization with neutral sodium carbonate solution (0.2 per cent) brought out the precipitate. This is consistent with the result of test 1. However, this precipitate was not soluble in excess sodium carbonate solution, as metaproteins generally are. The result of this test does not seem to rule out the presence of metaproteins.

4. After the previously boiled precipitate was cooled, addition of 0.4 per cent hydrochloric acid did not cause it to dissolve. This is consistent with the behavior of metaproteins.

5. Drop by drop addition to the precipitate of a saturated solution of ammonium sulfate caused it to dissolve. This is not what should happen with metaproteins.

6. After the precipitate was dissolved with 0.4 per cent hydrochloric acid, addition of an equal volume of a saturated solution of ammonium sulfate did not provoke the appearance of a precipitate, as it should with metaproteins.

Comment.—The tests just described revealed the presence of proteins. The classification of the proteins is difficult, since a careful consideration of the results of the tests shows a contradiction between them, which is not surprising when one reviews the literature on vegetable proteins. Nonetheless it may be concluded that the proteins are not large molecule proteins. They appear, rather, to be derived proteins, with characteristics similar to those of acid metaproteins and peptones, perhaps because of prolonged hydrolysis in an acid medium. This conclusion is based on the following observations:

(*a*) The proteins of coconut water are not flocculated by the addition of a saturated solution of ammonium sulfate. Peptones are the only proteins not flocculable by this salt in saturated solution.

(*b*) On addition of 0.4 per cent hydrochloric acid to the precipitated proteins, they are dissolved, and they precipitate again on addition of and neutralization with sodium carbonate solution. This reaction is compatible with the presence of metaproteins.

(*c*) After the precipitate is dissolved with 0.4 per cent hydrochloric acid, boiling does not produce a coagulum; neutralization with 0.2 per cent sodium carbonate solution after cooling again brings out the precipitate. This is also consistent with the presence of metaproteins.

(*d*) Addition (after cooling) of 0.4 per cent hydrochloric acid to the previously boiled precipitate does not cause it to dissolve. This reaction, together with the previous two, seems to bear out the possibility of the presence of acid metaproteins.

TABLE 1.—*Amino Acids of Coconut Water and of Cow's Milk* *

Amino Acids	Water	Milk
Glutamic acid	9.76 -14.50	20.36
Arginine	12.75	3.75
Leucine	1.95 - 4.18	10.64
Lysine	1.95 - 4.57	7.94
Proline	1.21 - 4.12	7.04
Aspartic acid	3.60	4.87
Valine	....	7.20
Tyrosine	2.83 - 3.00	5.81
Alanine	2.41	1.89
Histidine	1.95 - 2.05	2.51
Phenylalanine	1.23	3.50
Serine	0.59 - 0.91	0.69
Cystine	0.97 - 1.17	0.57
Tryptophan	.....	2.20

* Values are expressed in grams per hundred grams of dried proteins.

IMPORTANCE OF THE AMINO ACIDS FOUND IN THE PROTEINS OF COCONUT WATER

It is obvious that proteins of the nature postulated must contain amino acids, and we set out to demonstrate this by means of hydrolysis of the protein molecule.

Table 1 lists the amino acids found, with values expressed in grams per hundred grams of dry proteins. These values are compared with those in cow's milk. It may be seen that there is a greater percentage of arginine, alanine, cystine and serine in coconut water than in cow's milk. This should not be construed as meaning that coconut water is superior to the latter essential food, which is irreplaceable for proper nutrition. It is merely an interesting fact.

The high percentage of amino acids in coconut water does mean, however, that nature has made this water more than a mere suspension of electrolytes, as was heretofore empirically accepted. It contains substances now considered as essential, including lysine, cystine, methionine, valine, leucine, tryptophan, phenylalanine and histidine. Such amino acids have been assigned an important role in modern

human physiopathology, from the standpoint of cellular function, of the physicochemical phenomena in the obscure problem of immunity and of the intricate defense mechanisms; some of them act as antitoxins. Furthermore, medical literature contains reports of the use of these substances in the treatment of ulcers, of muscular dystrophies and, more recently, of the nephrotic syndrome of the child, although as Re, of Argentina, said in a recent and interesting report, to time and experience must be left the testimony of their utility and of the accuracy of the hypotheses postulated in this chapter of therapeutics.

The methods employed for the determinations of the amino acids, except for some pertinent modifications introduced by Dr. Fernandez Flores, were those recommended by Mr. Richard G. Block, of the

TABLE 2.—*Amino Acids in Proteins of Coconut Endosperm and of Coconut Water* *

	Endosperm	Water
1. Glutamic acid	19.07	9.76 -14.50
2. Arginine	15.92	12.75
3. Lucine	5.96	1.95 - 4.48
4. Lysine	5.80	1.95 - 4.57
5. Proline	5.54	1.21 - 4.12
6. Aspartic acid	5.12	3.30
7. Alanine	4.11	2.41
8. Valine	3.57	
9. Tyrosine	3.18	2.83 - 3.00
10. Histidine	2.42	1.95 - 2.01
11. Phenylalanine	2.05	1.23
12. Serine	1.76	0.59 - 0.91
13. Cystine	1.44	0.97 - 1.17
14. Tryptophan	1.25	
15. Leucivaline	0.64	

* Values are expressed in grams per hundred grams of dried proteins.

chemistry department of the New York State Psychiatric Institute and Hospital, in a monograph edited in 1938.

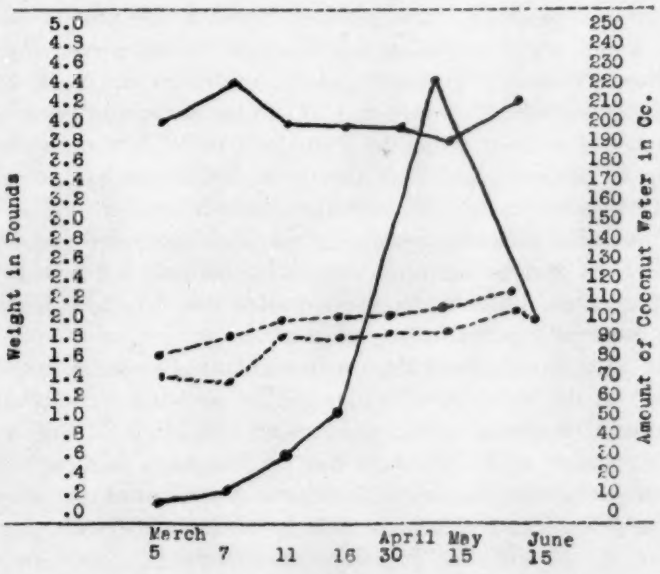
RELATION BETWEEN THE PROTEINS IN THE ENDOSPERM AND THOSE OF THE COCONUT IN THE WATER

As soon as one compares the proteins of the endosperm with those found in the water (table 2), one is struck by the similarity in their composition. This tends to confirm the theory that the endosperm of the coconut is a result of adaptation and transformation of the constituents of the water. However, the protein of the endosperm is not a derived protein, like that of the water, but a globulin of definite chemical characteristics. And though, as we repeat, we have not found a report of any detailed study of the protein of the water, this does not hold true for that of the endosperm, a fact gleaned from intensive study of literature published between 1891 and 1940. The endosperm globulin has been exhaustively studied by Johns, Finks and Paul, of the United States, who demonstrated its high nutritive value when they

proved that young rats fed coconut endosperm develop normally. These authors stated that this protein is superior to other vegetable proteins, owing to its high content of lysine, which is present only in small amounts in the proteins of the majority of cereals.

EXPERIMENTAL ANAPHYLAXIS IN THE RABBIT AS A MEANS OF DETERMINING THE PRESENCE OR ABSENCE OF SENSITIZING PROTEINS

The accompanying chart summarizes this experiment. Each of 3 animals received (no. 1 intravenously, no. 2 subcutaneously and no. 3 intraperitoneally) the same quantities of coconut water, namely 5, 10,



Attempt to produce experimental anaphylaxis in rabbits.

20, 50, 100 and 200 cc. The amounts of coconut water injected into each animal expressed in cubic centimeters per unit of body weight may be expressed thus: rabbit 1 (intravenously), 1.25 cc. minimum and 50 cc. maximum per pound (2.75 and 110 cc. per kilogram); rabbit 2 (subcutaneously), 3.57 cc. minimum and 142.8 cc. maximum per pound (7.86 and 314 cc. per kilogram); rabbit 3 (intraperitoneally), 3.12 cc. minimum and 125 cc. maximum per pound (6.7 and 275 cc. per kilogram). Injections were given from March 5 to June 15, a period of three months and ten days, the intervals from the first injection being two, six, eleven, fifty-six, seventy-one and one hundred and two days.

In none of the animals was any important alteration noticed as a result of the injections, except in rabbit 1, which had a thermal rise of 0.4 to 0.5 degree (C.), anal temperature, with every injection (the temperature being taken immediately after each one).

The only necropsy performed was on rabbit 1. No macroscopic or microscopic lesions were found.

From these observations we may infer that coconut water does not produce sensitization and that the amounts injected into the experimental animals are relatively harmless.

HISTORICOBIBLIOGRAPHIC SURVEY OF MEDICAL USE OF COCONUT WATER

Desirous of learning from medical literature the possible uses of coconut water, we consulted numerous publications, principally those of the Food Research Division, Bureau of Chemistry and Soils, Department of Agriculture, Washington, D. C. Our survey included reports concerning the coconut published from 1891 to 1935, except literature referring to oils extracted from this fruit, which was not considered. Medical literature up to 1940 was also studied.

We offer the following résumé of the only literature found by us which, even if it does not refer directly to coconut water, aids us in substantiating our belief in the usefulness of this substance in medical practice, especially in the feeding of infants.

Klein (1933) mentioned the communication of Gesteira and Bahia, of Brasil, on the value of milk obtained by pressing coconut meat in the treatment of infants with toxi-infectious conditions. These authors found it of value as a temporary diet for nurslings studied by them.

Axtmayer (1932) discussed the vitamin B content of coconut water. In an interesting experiment on rats he proved that the water is a good source of the B vitamins, especially of vitamin B_2 (now known as riboflavin).

In Kugelmass' book "Newer Nutrition in Pediatric Practice" (1940, page 75) a content of 56 international units of vitamin B_1 (thiamine) for each 50 Gm. of fresh coconut is given.

The foregoing facts, and even more its own composition, suggest multiple uses to which coconut water might be put. But there is a sorry absence of data with regard to its medical application, in contrast to the wealth of material on its commercial uses, which have been exhaustively studied with respect to the entire fruit, from which oils are extracted to manufacture oleomargarine, the remainder still serving, after its passage through the mills, as an excellent food for cattle. Johns, Fink and Paul as far back as 1919 emphasized the nutrient value of coconut glóbulin, demonstrated by its action as sole nourishment of young rats.

WAYS OF USING COCONUT WATER IN CLINICAL PEDIATRICS

The foregoing observations would have merely academic value if clinical practice had not convinced us of the merits of coconut water in nutrition. The purpose of this modest contribution is our desire to share what our limited experience has shown us in the hospital, in the dispensary and in our private practice.

First let us give the reasons on which we base our use of mixtures of coconut water and milk: Coconut water is a natural, sterile and acid solution containing salts, proteins, carbohydrates and neutral fats. Its composition indicates its qualities as a nutriment. Particularly, the amino acids present in it show the importance of its derived proteins. Its organic acidity implies the possibility of modification of the buffer substances in milk, thereby reducing coagulum tension. Its sugars and fats may increase its energy-producing value; even though this argument may be slightly theoretic, owing to the relatively small proportion of these elements that it contains, it is nonetheless worthy of consideration.

For a long time physicians have been trying to increase the digestibility quotient of artificial milks, employing to this end, in their unremitting efforts, acids and bases, salts and colloids. In recent times, however, acid milks have had the greatest support and popularity, especially in the United States, with Marriot as leader. Therefore, what can be argued against use of a natural acid element that can be employed as a substitute for the usual organic acids in acid milk mixtures?

In tables 3 and 4 we present data on a number of infants fed our evaporated and milk and coconut water mixture, cow's milk being excluded, as we have not employed it for our patients. Proportions and calculations for the use of this mixture are substantially the same as for milks acidified with lactic acid.

Of the 23 infants included in table 3, 15 (65.25 per cent) were cared for at the dispensary and 8 (34.75 per cent) in private practice. All the infants were considered as normal at the physical examination and had no familial or personal history of a pathologic condition. Ninety-one and three-tenths per cent had one or two stools daily, the feces resembling in consistency and appearance those of children fed lactic acid milk. For only 1 child was feeding of our milk mixture discontinued (because of diarrhea), and this patient had a coexisting nasopharyngitis. Eight per cent of the infants were constipated, and it was necessary to resort to administration of fruit juices and use of suppositories. Of 50 infants selected as possible subjects among the patients that came daily to the workers' maternity dispensary, 25 (nurslings) were discarded because their families could not pay for the

coconut water or because of the risk of poor cooperation due to the poor education of some of the lower class people in Cuba and their lack of refrigerators in which to keep the mixture of milk and coconut water at low temperature, which is essential to prevent fermentation of the water.

TABLE 3.—*Normal Infants Fed a Coconut Water and Evaporated Milk Mixture*

No.	Age, Days	Sex	Race	Weight					Stools per 24 Hr.	Constipation	Diarrhea
				Admission	1 Mo.	2 Mo.	4 Mo.	6 Mo.			
1	5	M	N	6.80	7.10	9.00	14.40	16.80	4	0	0
2	5	M	W	8.00	9.50	10.80	13.15	17.20	2	0	0
3	7	F	W	7.20	8.12	9.15	14.30	16.90	5	0	0
4	7	M	W	6.50	8.15	10.13	16.50	18.00	3	0	0
5	9	M	W	9.10	10.20	11.40	13.15	15.80	1	+	0
6	11	F	N	7.40	8.12	10.12	12.14	15.10	4	0	0
7	11	F	W	8.30	9.10	10.50	13.20	15.15	2	0	0
8	12	M	W	7.10	9.40	11.20	14.00	16.15	1	++	0
9	12	M	W	6.15	8.12	10.80	13.20	15.40	5	0	0
10	14	F	W	8.10	9.10	11.15	14.10	16.30	3	0	0
11	14	M	N	9.20	10.40	11.60	14.20	17.00	2	0	0
12	14	M	W	7.10	9.15	11.70	15.00	16.12	3	0	0
13	14	F	W	7.00	8.10	10.00	13.20	15.15	2	0	0
14	14	M	W	7.80	10.00	11.80	14.00	16.70	2	0	0
15	16	M	N	8.15	10.12	12.20	14.30	16.10	2	0	0
16*	16	..	..	....	.....	.....	.....	.....	..	0	++++
17	16	M	N	7.15	9.00	10.10	14.70	16.20	3	0	0
18	17	F	W	8.50	8.15	11.40	15.80	17.60	4	0	0
19	17	M	W	9.00	10.70	11.15	14.60	16.00	5	0	0
20	17	F	W	9.60	10.40	11.80	13.60	15.70	2	0	0
21	20	M	W	10.40	11.15	13.60	15.70	17.15	3	0	0
22	21	M	W	9.70	11.50	13.20	15.15	17.40	1	0	0
23	22	M	W	10.15	12.50	13.12	15.10	16.20	4	0	0

* Use of the mixture was discontinued because of diarrhea.

TABLE 4.—*Infants with Pathologic Conditions Fed a Coconut Water and Evaporated Milk Mixture*

Condition on Admission	Age, Mo.	Sex	Race	Weight		Days in Hospital
				Admission	Discharge	
Pellagra	13	F	W	12.8	18.5	60
Pellagra	15	F	W	15.6	20.7	90
Dystrophia	6	F	W	8.4	10.15	16
Dystrophia	4	M	W	9.2	13.10	86
Dystrophia	8	M	N	13.5	16.80	45
Anemia, malnutrition and diarrhea	10	F	W	18.4	18.10	15
Anemia, malnutrition and diarrhea	8	M	N	17.6	16.50	10
Anemia, malnutrition and diarrhea	5	M	W	14.0	15.10	30
Anemia, malnutrition and diarrhea	9	M	W	18.10	19.00	20
Anemia, malnutrition and diarrhea	15	F	W	25.15	24.80	6

Table 3 shows the satisfactory increase in weight of the normal infants studied. From our service at the Mercedes Hospital we report only on the patients considered interesting because of their clinical picture, those for whom ordinary acid or nonacid milks would be suitable being discarded.

We shall describe the case of patient 3 of table 4, since we consider it interesting and illustrative of the method followed in similar cases.

G. H. C., a white girl 6 months old, weighing 8.4 pounds (3,805 Gm.), was admitted to the hospital because of malnutrition, diarrhea and anemia. There was nothing abnormal in the familial history. The child had weighed 7.12 pounds (3,225 Gm.) at birth, and the birth had been normal. She had been breast fed for only one month, this type of feeding having been abandoned because of hypogalactia of the mother and diarrhea of the patient. She had not been well since and had passed numerous greenish, fermentative stools. Throughout this illness she had been given numerous milk formulas, evaporated milk, cow's milk, sweetened condensed milk, mare's milk, powdered dried milk and evaporated milk in a poorly balanced solution. A consideration of this diet explains her malnutrition (due to hunger) and her diarrhea. She had never taken vitamins or fruit juices in sufficient amounts.

On her admission to the Manuel de la Cruz ward (Chair of Pediatrics Service) at the Mercedes Hospital, her physical examination revealed an acute dystrophic condition due to deficient nutrition. Her hair was brittle and discolored, resembling that of a child with pellagra. Her skin was dry, and the panniculus adiposus was poor; the abdomen was rounded and protuberant. She was noticeably irritable, and her voice was thick when she cried.

The calcium content of the blood was 10.1 mg. per hundred cubic centimeters and the phosphorus content 2.45 mg. The ascorbic acid content was 0.494 mg. The red blood cell count was 3,130,000 and the white cell count 9,500. There were 40 per cent segmented neutrophils, 1 per cent stab neutrophils, 53 per cent lymphocytes and 6 per cent monocytes. The hemoglobin content was 63 per cent and the color index 1.01. The red cells showed anisocytosis and anisochromia. The urine was normal. The feces were essentially normal.

The patient was given a 5 per cent solution of pectin, agar-agar and dextrose (pectilose) in evaporated milk and coconut water. After a week mashed Cuban velvet bananas and half an egg yolk daily were introduced into the diet. Liver extract and ascorbic acid were given parenterally and ferrous sulfate and percomorph liver oil by mouth.

After the third day of this treatment the patient's diarrhea disappeared, her stools acquiring a normal appearance and not exceeding three each twenty-four hours. On her discharge, two weeks later, she had gained 2.1 pounds (951 Gm.). Two months later she weighed 15.08 pounds (6,831 Gm.), a total gain of 7.2 pounds (3,262 Gm.). Physical examination, study of the blood cells, urinalysis, the Kjadi test and determinations of ascorbic acid and of calcium and phosphorus in the blood gave completely normal results.

The cases of the 2 infants with pellagra may be considered typical. Each had received deficient feeding, with repeated and unnecessary changes in their milk. Their vitamin intake was as deficient as their unbalanced diet, as is common among the country people and lower classes in Cuba. Both patients had had diarrhea.

The children listed as having dystrophies had had equally deficient diets but were without typical pellagrous manifestations. All 3 had suffered from diarrhea in different periods of their illness, according to their clinical histories, but only 1, patient 3 of table 4, presented a characteristic glairy diarrhea, without pus or blood cells.

Careful scrutiny of table 3 reveals that, in addition to the tolerance for evaporated milk acidified with coconut water that was manifested,

the increase in weight and the general condition of the infants were excellent. Besides the milk formula, all these children were given adequate amounts of vitamins, consisting daily of 10 drops of an oil solution of vitamins A and D (adexolin) containing 12,000 international units of vitamin A and 2,000 international units of vitamin D per cubic centimeter and 50 mg. of ascorbic acid.

In the cases detailed in table 4 the treatment was based on the symptoms and the underlying pathologic condition of the patients, coconut water being included in the milk formulas just as water alone or water acidified with lactic acid would have been, to increase the digestibility coefficient by modification of the buffer substances in the milk.

The purpose of the foregoing discussion and tables is not to present statistics, which would obviously be insufficient, but merely to indicate

TABLE 5.—*Mineral Content of Coconut Water (12 samples)*

No.	Ripe	Unripe	Specific Gravity	Calcium, Mg. per 100 Cc.	Chlorine, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.
1	+	..	1.025	32	140	5.5	220	...
2	..	+	1.022	31	110	8.3	166	5.6
3	..	+	1.018	29	105	6.9	142	5.7
4	+	..	1.026	29	120	...	158	5.6
5	+	..	1.025	..	160	8.9	162	5.5
6	..	+	1.016	31	120	7.5	154	5.7
7	..	+	1.018	27	160	7.6	146	...
8	..	+	1.021	..	145	9.0	136	5.7
9	+	..	1.020	29	130	7.9	130	...
10	+	..	1.022	46	125	13.0	134	5.6
11	..	+	1.016	30	110	6.9	156	5.6
12	+	..	1.026	30	150	7.5	200	5.7

the value of coconut water and the tolerance that is manifested to it and the advantage of naturally acidified milk with, in addition, the important nutritional factors it abundantly contains.

POSSIBILITY OF PARENTERAL INJECTION OF COCONUT WATER AND SCIENTIFIC BASIS FOR IT

The density of coconut water (1.020 to 1.026) is comparable to that of blood plasma. Injection of coconut water intravenously, intraperitoneally and subcutaneously has shown that it does not contain complex molecule proteins and is therefore incapable of producing anaphylactic shock. Study of its proteins reveals that they are derived proteins, of the order of acid metaproteins and/or peptones, rich in varied amino acids, including lysine, leucine, cystine, phenylalanine, histidine and tryptophan, essential for proper nutrition. Its electrolytes comprise calcium, sodium, potassium and magnesium salts of organic acids, chlorides and phosphates, the highest content being in potassium (table 5).

The conclusion that coconut water can be injected may therefore be easily reached. However, to determine in which cases this should be done and what benefits may be derived from the injection would require a thorough study, which does not fit into the scheme of this preliminary communication.

The patients used to determine their tolerance to injection of coconut water were mostly patients hospitalized for various causes who did not have a disorder of acid-base metabolism or manifestations of systemic disturbance when they were given the injections.

Coconut water for parenteral injection was aseptically obtained from the fruit by means of an ordinary transfusion set, vacuum and air filtration being secured with a small suction pump like those employed for aspirators in operating rooms.

TABLE 6.—*Patients to Whom Coconut Water Was Administered by Venoclysis*

No.	Age, Yr.	Sex	Race	Weight, Kg.	Coconut Water per Kg., Cc.	Total Coconut Water, Cc.	Fluids per 24 Hr., Cc.	Urinary Output, Cc.	Time of Maximum Output, Hr.	Temperature, F.	Chills	Blood Chemistry	Urine	Blood Pressure
1	6	F	W	12.2	20.2	250	.....	.....	..	38	0	..	N	..
2	7	M	W	10.0	24.8	250	.....	.....	..	37.6	0	N	N	..
3	7	M	N	20.7	9.6	200	.....	.....	..	39.1	+	N	N	..
4	8	M	W	29.2	30.7	900	1,870	1,980	2	N	0	N	N	..
5	9	M	W	25.0	20.0	500	1,120	1,850	16	N	0	N	N	..
6	9	M	W	25.0	20.0	500	1,000	1,080	1	37.4	0	N	N	..
7	10	M	W	28.3	17.6	500	1,330	830	3	N	0	..	N	N
8	12	M	N	23.0	21.7	500	1,120	1,340	3	N	0	N	N	N
9	13	F	W	35.9	13.9	500	1,800	2,110	11	N	0	N	N	..
10	14	M	W	34.6	14.4	500	1,000	740	6	37.3	0	..	..	N
11	36	F	N	44.2	11.3	500	1,175	840	6	N	0	..	N	N
12	50	F	W	52.0	9.6	500	1,200	980	4	N	0	..	N	N

Venoclysis.—Data on patients treated by venoclysis are presented in table 6. The fluid was administered at the rate of 30 to 40 drops per minute for a period ranging from three to six hours.

In 5 of the 12 patients (41.66 per cent) a rise of temperature was manifested, which did not, however, reach 39 C. (102.2 F.) except in patient 3. This patient was a child admitted to the hospital for acute appendicitis and operated on the day preceding the injection. His temperature when venoclysis was started was 38 C. (100.4 F.). He was vomiting frequently, the vomitus being bilious. After three hours of the injection his temperature had risen to 39.1 C. (102.38 F.) and he had chills and headaches. Venoclysis was stopped at this time, as it could possibly have been the cause of the increased fever and chills, and no further treatment other than application of an ice bottle to the head was given. Twelve hours after the injection was discontinued, the general picture had improved 90 per cent, with a drop of temperature to 37.6 C. (99.68 F.), and the child's disposition was pleasant. Twenty-

four hours later his temperature had not risen above 37.5 C. (99.5 F.) and vomiting had ceased. Chemical examinations of the blood were made before the venoclysis and up to two hours after the injection was discontinued and were reported as giving normal results. The acid-base equilibrium was not altered, perhaps because of the injection of coconut water. The chemical determinations made in the cases reported here included determination of the p_H, total chlorine, red blood cell–plasma chlorine index, carbon dioxide concentration index, urea and sugar.

Patient 1 of table 6 had a condition corresponding to the Still-Chauffard syndrome. She had had a continuous remittent fever, the temperature oscillating between 37 and 38 C. (98.6 and 100.4 F.). Hence the temperature reported in the table cannot be considered a result of the venoclysis.

Patients 2 and 6 had temperatures not exceeding 37.6 C. (99.68 F.) and did not present any objective or subjective signs of unfavorable reaction. The temperature returned to normal four hours after the injection was begun.

The case of patient 10 is interesting because she suffered from a compensated nephronephritis. Although her temperature reached only 37.3 C. (99.14 F.) one hour after venoclysis was started, this child had a feeling of warmth in her face, which was flushed. Her urinary elimination did not increase, being only 740 cc. in twenty-four hours, although her intake of fluid, both oral and parenteral, in the same period had been 1,000 cc. The maximal elimination occurred at the sixth hour after the injection was started and did not exceed 200 cc.

Patients 11 and 12 were adults, hospitalized in ward "Sta. Margarita" of Professor Casuso's gynecologic service. Patient 11 was operated on three days previous to the injection, a total colectomy having been performed, with exteriorization of the distal branch. Patient 12 had been appendectomized the previous day. Both patients had received a venoclysis of sterile physiologic solution of sodium chloride, which was stopped two hours after it was begun on account of a pronounced febrile reaction and intense chills. In these two patients, as is pointed out in table 6, no unfavorable reaction was noted during or following injection of coconut water.

For 7 of the 12 patients (58.33 per cent) chemical studies of the blood (the determinations specified earlier in this section) were reported as giving normal results. Determinations were made both before and after the injection.

In 8 of 9 cases in which the elimination curve could be studied the urine was reported as normal. (Urinalysis was partial and referred only to: [physical] color, appearance, p_H, specific gravity and volume; [chemical] albumin, dextrose, urobilinogen, biliary salts and pigments,

and [microscopic] sediment. These studies were made on the various samples collected in a twenty-four hour period.)

In 5 of the 9 cases studied (55.5 per cent) urinary elimination in twenty-four hours surpassed the oral and parenteral intake of fluid, with a maximum of 730 cc. and a minimum of 80 cc. above the total intake.

Hypodermoclysis.—Hypodermoclyses were made solely to determine the response of the subcutaneous connective tissue. Data are presented in table 7.

Patients 11 and 12 received the injection while in full febrile reaction. Patient 9 had rhinopharyngitis with high fever. He received 100 cc. of coconut water in the external part of each thigh without

TABLE 7.—*Patients to Whom Coconut Water Was Administered by Hypodermoclysis*

No.	Age, Mo.	Sex	Race	Wt., Lb.	Wt., Kg.	Coconut Water per Lb., Cc.	Coconut Water per Kg., Cc.	Total Coconut Water, Cc.	Temperature	Local Reaction
1	2	M	N	4.90	2.27	24.04	44.50	200	39.8	0
2	4	M	W	14.00	6.36	14.28	31.40	200	N	+
3	4	F	W	13.30	5.99	7.58	16.60	100	N	+
4	8	F	N	17.40	7.84	11.40	25.50	200	N	+
5	9	M	W	19.00	8.60	13.10	29.00	250	N	0
6	9	M	W	18.90	8.50	5.20	11.70	100	N	0
7	9	M	W	16.40	7.40	6.09	13.50	100	N	0
8	10	M	W	17.60	8.00	13.08	28.70	230	N	+
9	12	M	W	21.20	9.60	9.43	20.70	200	N	0
10	12	F	N	25.00	11.30	8.00	17.60	200	N	0
11	12	M	W	14.90	6.70	33.50	73.60	500	39.4	0
12	72	F	W	26.90	12.27	18.90	40.70	500	37.5	0
13	132	F	N	85.10	38.70	2.64	5.70	225	N	0

inflammatory reaction. Absorption was slow, however. Patient 1 was a premature baby with congenital syphilis and acute bronchopneumonia, who died three hours after admission to the hospital.

SUMMARY AND CONCLUSIONS

Even though different authors have studied intensively the proteins of the coconut's endosperm and also the amino acids, no reference was found in the literature to the proteins and amino acids of coconut water. Moreover, to our knowledge, there has been no work treating of the medical applications of coconut water.

The investigation reported here was concerned fundamentally with an analytic chemical study of the proteins of coconut water, which resulted in isolation and determination of the relative amounts of twelve amino acids. The physicochemical nature of coconut water, especially the character of its derived proteins and the fact that it contains most of the amino acids today considered as essential, constitutes a scientific

argument for its value in nutrition and suggests valuable therapeutic applications.

In our opinion, the use of mixtures of coconut water and evaporated milk opens new possibilities in infantile dietetics. But this should not be construed as meaning that such mixtures may be employed regularly and indiscriminately. Their use should be governed by conscientious clinical criteria, which must perforce be different in each case.

Intravenous administration of this substance must be studied further and judged by a greater clinical experience. We do not pretend to have done more than show its possible applications, in view of the few cases we had available for study. Its subcutaneous administration produced in 4 of the 13 patients studied a transitory local reaction, inflammatory and painful, comparable to that produced in many instances by a 5 per cent solution of dextrose.

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CREATINURIA IN INFANCY AND IN CHILDHOOD

II. CREATINURIA OF PREMATURE INFANTS

ELEANOR MARPLES, B.A.

NEW YORK

Paffrath and Ohm [1] in 1933 reported the virtual absence of creatine in the urine of premature infants, and Levine and I [2] also found little or no creatine in casual specimens of urine from 6 premature infants who were receiving human milk. These subjects differed from full term infants receiving cow's milk, who excreted creatine in amounts ranging from 6 to 49 per cent of the total creatinine excretion.[2]

Studies of the daily creatine and creatinine excretion of premature infants who were receiving formulas of human or cow's milk and of full term infants of comparable age receiving cow's milk form the basis of the present report. The assembled data permit an analysis of the effect of protein intake on the creatine and creatinine excretion of premature and full term infants fed similar amounts of protein in the form of cow's milk.

METHODS AND MATERIAL

Subjects.—Forty healthy male premature infants were studied.[3] Thirty-three of the infants were white; 7 were Negro. Their birth weights varied from 1.25 to 2.33 Kg. They were from 6 to 66 days old and weighed from 1.45 to 2.70 Kg. at the onset of observations. Results of serologic examination of the blood for syphilis were negative for all of the infants. Data on 13 full term infants are also

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From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

1. Paffrath, H., and Ohm, W.: Zur Frage der Kreatinurie des Frühgeborenen, Ztschr. f. Kinderh. **54**:377, 1933.

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3. Detailed studies of the nitrogen metabolism of 5 of the premature infants (T. A., H. B., J. G., W. J. and V. R.) were reported in a previous paper (Gordon, H. H.; Levine, S. Z.; Wheatley, M. A., and Marples, E.: Respiratory Metabolism in Infancy and in Childhood: XX. The Nitrogen Metabolism in Premature Infants—Comparative Studies of Human and Cow's Milk, Am. J. Dis. Child. **54**: 1030 [Nov.] 1937).

included for the purpose of comparison. These infants were from 18 to 72 days of age and weighed 2.78 to 4.48 Kg. at the onset of observations.

Diets.—Diets usually accepted as suitable for premature infants were employed, and they sufficed to produce a steady gain in weight throughout the experimental period, averaging 30 Gm. per day. When the infants were about 2 weeks old, vitamin A and D concentrates were added to the diet.

Three types of diet were used. The first consisted of human milk, with relatively low protein intake (2.4 Gm. per kilogram per day). The other two types were of cow's milk; one had a relatively low protein content, of 3.1 Gm. per Kg. per day, and the other provided an average of 5.3 Gm. of protein. The full term infants all received diets of the latter type, with an average protein intake of 5.4 Gm. per Kg. per day.

Chemical Analyses.—Thoroughly mixed samples of the powdered milk and pooled daily samples of the liquid cow's milk and human milk were analyzed in triplicate for nitrogen by the macro-Kjeldahl method.[4] The protein content was estimated by multiplying the value for nitrogen by 6.25.

The technic for collecting specimens of urine was given in a previous paper.[2] The periods were accurately timed and the results calculated on the basis of twenty-four hours.

The urine was analyzed in duplicate for nitrogen by the macro-Kjeldahl method. Preformed creatinine was determined by the Folin method.[5] Creatine was converted to creatinine by adding hydrochloric acid and evaporating to dryness on a steam bath. The results are expressed in the form of coefficients, i. e. milligrams of nitrogen per kilogram of body weight per twenty-four hours excreted as creatinine and creatine, respectively.

A number of the infants excreted parahydroxyphenylpyruvic acid and other products of the intermediary metabolism of tyrosine and phenylalanine when receiving diets of relatively high protein content.[6] The keto acid also gave the Jaffé reaction and thus interfered in the determination of creatinine. It could be removed by extracting acidified urine with ether, the creatinine being determined in the ether-extracted urine. This procedure was used for infants R. E., L. F., R. E. S. and F. Z. A second method, which was used more frequently, depends on the difference in behavior of creatinine and parahydroxyphenylpyruvic acid when treated with Lloyd's reagent (an aluminum silicate), the former being selectively adsorbed. The adsorbed creatinine is then eluted from the reagent with magnesium oxide, the technic used being essentially that devised by Gaebler[7]

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4. The human milk used for infants J. D., I. F., L. F., E. H., F. J. L., R. L., E. P., R. S. and F. Z. and the evaporated milk used for the full term infants P. A. and A. T. were not analyzed. For these, the average values of previous determinations were used: human milk 0.198 and evaporated milk 1.0212 Gm. of nitrogen per hundred grams of milk.

5. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, pp. 518-602.

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7. Gaebler, O. H.: Further Studies of Blood Creatinine, J. Biol. Chem. **89**:451, 1930.

for his study of blood filtrates. This method, used on 23 specimens of urine containing no keto acid, yielded from 72 to 86 per cent of the creatinine originally present, with an average yield of 80 per cent. Values for creatinine obtained with this procedure were therefore corrected by this factor.

Total creatinine (preformed creatinine plus creatine) could be determined directly, since after treatment of the urine with acid and heat to convert creatine to creatinine parahydroxyphenylpyruvic acid no longer gave a color with an alkaline (sodium) picrate.

RESULTS

Tables 1 to 5 present data on the nitrogen intake and urinary nitrogen, creatine and creatinine for a total of five hundred and ninety-two days of observation of 40 premature infants and ninety-two days for 13 full term infants. The infants have been divided into four groups:

Group 1: Premature infants receiving diets of human milk with a relatively low protein content (average intake 383 mg. of nitrogen per kilogram per day, or 2.4 Gm. of protein). The data for this group comprise 102 daily analyses for 15 infants (table 1).

Group 2: Premature infants receiving diets of cow's milk with a relatively low protein content (average intake 495 mg. of nitrogen, or 3.1 Gm. of protein, per kilogram per day). Four premature infants, all of whom had received a constant diet for a foreperiod of at least three days before the onset of observations, were studied for a total of fifty-four days (table 2).

Group 3: Premature infants receiving diets of cow's milk with a relatively high protein content (average intake 856 mg. of nitrogen, or 5.4 Gm. of protein, per kilogram per day). Table 3 presents the results of a total of four hundred and thirty-six days' study of 35 infants, all of whom had received a constant diet for a foreperiod of at least three days before the onset of observations.

Group 4: Full term infants of ages comparable to the infants of the premature series receiving cow's milk formulas with a nitrogen intake similar to that of the premature infants in group 3 (831 mg. of nitrogen, or 5.2 Gm. of protein, per kilogram per day). Ninety-two analyses were performed on urine from 13 infants (table 4).[8] The results are summarized in table 5.

The Excretion of Creatinine.—The daily excretion of creatinine of both premature and full term infants is not an absolutely constant figure. Since Folin[9] first pointed out the constancy of the creatinine

8. Data on the creatine metabolism of 4 of these infants (T. G., M. M., R. Sp. and W. W.) were reported in a previous paper.[2]

9. Folin, O.: Laws Governing the Chemical Composition of Urine, Am. J. Physiol. **13**:66, 1905.

excretion in the adult, other workers [10] have found it to be relative rather than absolute. Daily variations amounting to 10 per cent of the average in adults are not uncommon. Wang [11] and her co-workers

TABLE 1.—*Urinary Excretion of Creatine and Creatinine by Premature Infants Receiving Human Milk (Low Protein Diet)*

				Mg. of Nitrogen per Kg. per 24 Hours							
						Creatinine			Creatine		
Subject	Age, Days	Average Weight, Kg.	No. of Days Observed	Average Nitrogen Intake	Average Urinary Nitrogen	Average	Max.	Min.	Average	Max.	Min.
R. J.	14-15	1.49	2	404	114	4.52	4.7	4.4	0.57	0.7	0.5
F. J. L.	17	1.60	1	347	82	4.60	...	...	0.85	...	...
H. B.	16-21	1.61	10	490	85	4.58	5.1	4.3	0.01	0	...
R. L.	7- 8	1.62	2	320	57	4.07	...	...	0.77	...	...
W. D.	11-17	1.81	7	453	120	4.62	5.7	4.0	0.71	1.1	0.4
F. Z.	13-22	1.82	4	397	96	3.78	4.8	3.2	0	0	...
V. R.	18-23	1.93	6	443	108	4.56	4.8	4.4	0.12	0.2	0
S. P.	10	1.95	1	366	66	3.46	...	...	0.16	...	...
T. A.	19-24	1.97	6	361	71	3.88	4.1	3.7	0.49	0.7	0.3
E. P.	17-18	2.04	2	435	72	4.30	4.3	4.3	0.39	0.5	0.3
J. D.	13-17	2.06	3	345	75	3.94	4.2	3.5	0.02	0	...
L. F.	10-29	2.09	3	373	98	4.26	5.0	3.5	0.22	0.3	0
R. S.	11-12	2.10	2	380	86	3.86	4.0	3.7	0.39	0.6	0.2
A. P.	10-11	2.16	2	312	71	3.92	3.9	3.9	0.28	0.3	0.2
W. D.	31-44	2.34	14	429	116	4.38	4.9	3.8	1.32	2.6	0.4
V. R.	48-51	2.82	4	436	118	4.47	4.7	4.3	0.10	0.2	0
E. H.	42-66	2.98	23	340	108	4.20	4.7	3.4	0.12	0.4	0
E. H.	81-90	4.16	10	258	78	4.52	4.8	4.2	0.73	1.6	0
Average		2.14		383	90	4.22			0.40		
Total			102								

TABLE 2.—*Urinary Excretion of Creatine and Creatinine by Premature Infants Receiving Cow's Milk (Low Protein Diet)*

					Mg. of Nitrogen per Kg. per 24 Hours							
							Creatinine			Creatine		
Subject	Age, Days	Average Weight, Kg.	No. of Days Observed	No. of Days on Cow's Milk Before Onset of Observations	Average Nitrogen Intake	Average Urinary Nitrogen	Average	Max.	Min.	Average	Max.	Min.
W. J.	16-37	2.01	16	4	582	212	5.57	6.3	5.0	0.91	2.4	0
T. A.	28-36	2.23	9	3	517	133	4.03	4.3	3.7	0.07	0.2	0
J. C.	14-16	2.37	3	10	390	146	4.98	5.2	4.7	0.24	0.3	0.2
F. J. L.	22-59	2.40	23	3	565	220	4.81	5.3	4.3	0.44	0.9	0
J. C.	25-27	2.76	3	3	421	163	5.31	5.4	5.0	0.21	0.3	0.2
Average		2.35			495	175	4.94			0.37		
Total			54									

10. Hunter, A.: Creatine and Creatinine, New York, Longmans, Green & Co., 1928.

11. Wang, C. C.; Genther, I., and Hogden, C.: Metabolism of Adolescent Girls: III. The Excretion of Creatinine and Creatine, Am. J. Dis. Child. **51**:1268 (June) 1936.

TABLE 3.—*Urinary Excretion of Creatine and Creatinine by Premature Infants Receiving Cow's Milk (High Protein Diet)*

Subject	Age, Days	Average Weight, Kg.	No. of Days Observed	No. of Days on Cow's Milk Before Onset of Observations	Mg. of Nitrogen per Kg. per 24 Hours: Average Nitrogen Intake	Average Urinary Nitrogen	Creatinine: Average	Creatinine: Max.	Creatinine: Min.	Creatine: Average	Creatine: Max.	Creatine: Min.
R. J.	30-37	1.68	6	9	806	334	4.27	4.5	3.9	0.12	0.3	0
R. L.	13-15	1.90	3	3	801	242	4.59	...	...	1.54	...	...
R. G.	16-52	1.94	10	8	912	344	4.06	4.8	3.6	0.26	0.8	0
M. P.	11-16	2.02	6	4	881	485	5.14	5.7	4.8	1.10	2.0	0.3
W. D.	21-25	2.10	5	3	922	365	4.71	5.3	4.4	2.29	2.8	2.0
R. A. G.	19-39	2.15	14	19	850	346	5.14	5.7	4.6	1.47	2.5	0.6
J. Ch.	8-10	2.20	3	4	830	407	5.52	5.6	5.3	0.40	0.5	0.3
S. P.	14-21	2.21	6	3	824	417	4.69	4.9	4.4	0.83	1.5	0.1
D. M.	15-16	2.24	2	5	909	423	4.54	4.6	4.5	0.47	0.5	0.4
F. Z.	30-37	2.26	7	6	1,025	420	4.83	5.4	3.4	0.54	0.7	0.3
R. E.	10-33	2.28	9	5	947	454	4.93	5.2	4.4	2.41	2.8	1.3
R. M. G.	18-34	2.29	13	18	800	405	5.02	5.4	4.6	1.93	2.6	1.2
F. L.	9-14	2.30	4	3	702	154	5.05	5.6	4.7	1.71	2.1	1.2
E. P.	22-32	2.34	8	3	741	218	5.22	5.5	4.8	1.01	1.4	0.8
A. L. W.	19-20	2.34	2	11	935	340	4.42	4.5	4.3	0.37	0.4	0.3
W. B.	19-47	2.36	18	15	694	368	4.73	5.5	3.7	2.03	2.6	1.3
L. F.	25-26	2.36	2	12	942	480	4.28	4.4	4.1	1.04	1.3	0.8
J. Q.	13-14	2.37	2	6	873	411	5.00	5.2	4.8	0.03	0	...
I. F.	35-41	2.40	7	11	837	370	5.36	6.1	4.4	0.31	0.5	0.1
R. K.	22-27	2.40	6	21	737	394	5.53	6.3	5.2	0.81	1.8	0
H. C. A.	6-50	2.47	36	3	819	466	5.01	5.4	4.3	1.95	3.9	0
R. S.	16-22	2.47	4	3	722	284	5.05	5.6	4.4	1.83	2.4	1.0
R. E. S.	14-40	2.49	11	7	937	506	5.08	5.6	4.6	1.11	1.8	0
R. F.	17-40	2.51	25	5	1,004	508	6.05	6.6	5.4	3.54	5.0	0.8
A. P.	17-28	2.56	7	3	811	433	5.26	5.3	5.2	0.14	0.3	0
R. H. E.	10-37	2.60	13	3	996	628	5.73	6.7	5.1	2.64	6.0	0
J. S.	17-58	2.66	29	9	733	423	5.45	6.0	4.5	1.08	1.7	0
A. V.	17-61	2.70	33	6	1,013	557	5.31	6.1	3.2	2.71	4.9	0
P. J. A.	6-50	2.74	36	3	853	509	5.15	5.8	4.6	2.84	4.1	0.4
T. R.	21-62	2.82	29	19	840	533	5.44	6.7	4.9	0.91	2.7	0
J. Ca.	12-42	2.84	19	6	919	529	5.42	6.0	4.6	2.20	3.8	0.9
S. A.	66-90	3.13	13	56	781	435	4.73	5.2	4.1	3.40	4.2	2.3
J. G.	17-49	3.27	26	12	872	439	6.48	8.1	5.6	1.32	3.0	0
J. Ch.	40-63	3.58	16	3	830	582	5.52	6.4	5.0	1.33	2.8	0.5
E. H.	71-77	3.72	6	3	875	389	5.27	5.6	4.9	1.92	4.4	0
Average...		2.48			856	417	5.09			1.42		
Total.....			436									

TABLE 4.—*Urinary Excretion of Creatine and Creatinine by Full Term Infants Receiving Cow's Milk (High Protein Diet)*

Subject	Age, Days	Average Weight, Kg.	No. of Days Observed	No. of Days on Cow's Milk Before Onset of Observations	Mg. of Nitrogen per Kg. per 24 Hours: Average Nitrogen Intake	Average Urinary Nitrogen	Creatinine: Average	Creatinine: Max.	Creatinine: Min.	Creatine: Average	Creatine: Max.	Creatine: Min.
J. R.	36-57	2.89	8	34	894	614	5.38	6.0	4.6	1.86	2.6	1.3
R. Jo.	30-38	2.93	4	28	1,035	554	5.05	5.2	4.8	0.50	0.9	0.1
M. M.	20-28	2.94	4	19	852	447	5.37	5.8	5.0	3.36	3.7	3.1
J. O.	40-56	3.75	13	39	904	547	5.00	5.7	4.2	2.02	2.9	0.8
A. To.	72-85	3.85	8	62	743	452	5.48	6.2	4.6	3.47	4.5	2.2
R. Sp.	30-52	3.96	10	29	669	334	4.76	5.2	4.4	0.67	1.1	0.3
W. W.	28-29	3.96	2	27	788	400	5.14	5.5	5.0	1.77	1.8	1.8
R. Fr.	17-30	4.11	4	15	691	446	4.74	5.1	4.4	1.05	2.2	0.5
W. Do.	18-28	4.13	7	16	917	452	4.77	5.1	4.3	0.44	0.5	0.3
T. G.	54-71	4.30	7	53	653	383	5.21	5.3	4.9	3.69	4.4	2.6
P. A.	45-47	4.47	3	44	924	555	4.82	5.0	4.7	1.54	2.1	1.3
A. T.	27-48	4.62	14	27	804	497	4.62	5.0	4.4	1.48	2.1	1.1
R. C.	50-79	5.19	8	50	931	718	5.20	5.5	5.1	3.19	3.9	2.6
Average...		3.53			831	492	5.04			1.93		
Total.....			92									

found even greater variations in adolescent girls. In the premature infants, variations between maximum and minimum excretions of creatinine in a series of observations on individual infants ranged from 3 per cent (A. P.) (table 1) to 54 per cent (A. V.) (table 3) of the average obtained for the infant. The average variation calculated in this way from the data presented in tables 1 to 4 (including only infants studied five days or more) was 22 per cent of the individual average.

The average creatinine coefficient of normal infants has been reported by a number of workers, the values being 4.3 (Daniels and Hejinian[12]); 4.4 to 4.8 (Rougichitch[13]); 4.6 (Catherwood and Stearns[14]), and 4.9 (Marples and Levine[2]). The average creatinine

TABLE 5.—*Urinary Excretion of Nitrogen, Creatinine and Creatine*

Type of Infant	Type of Diet	Protein Content	No. of Infants	No. of Days Observed	Intake, Mg. of Nitrogen per Kg. per 24 Hours			Urinary Output, Mg. of Nitrogen per Kg. per 24 Hours		
					Nitrogen	Creatinine *	Creatine *	Nitrogen	Creatinine	Creatine
Premature	Human milk	Low	15	102	383	0.88	1.36	90	4.22	0.40
Premature	Cow's milk	Low	4	54	495	0.38	0.63	175	4.94	0.37
Premature	Cow's milk	High	35	436	856	0.65	1.08	417	5.09	1.42
Full term	Cow's milk	High	13	92	831	0.63	1.05	492	5.04	1.93

* The protein content of human milk was assumed to be 1.25 per cent (Holt, L. E., Jr., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York, D. Appleton-Century Company, Inc., 1940, p. 194) or 200 mg. of nitrogen per hundred cubic centimeters. According to Denis and Minot (Denis, W., and Minot, A. S.: The Non-Protein Nitrogenous Constituents of Cow's Milk, J. Biol. Chem. **38**:453, 1919. Methods for the Quantitative Determination of the Nitrogenous Constituents of Milk, ibid. **37**:353, 1919) 100 cc. of human milk contains 0.46 mg. of creatinine nitrogen and 0.71 mg. of creatine nitrogen per 100 cc. Therefore, in human milk, 1 mg. of protein nitrogen would be equivalent to 0.0023 mg. of creatinine nitrogen and 0.00355 mg. of creatine nitrogen. Similarly, cow's milk was considered to contain 3.5 per cent of protein and 0.43 mg. of creatinine and 0.71 mg. of creatine nitrogen per hundred cubic centimeters. One milligram of protein nitrogen would then be equivalent to 0.00077 mg. of creatinine and 0.00123 mg. of creatine nitrogen. The nitrogen intake was multiplied by these figures to give the creatine and creatinine nitrogen intakes.

coefficient for the full term infants in this series (5.04) agrees with these figures, as does the average coefficient of 5.09 for the premature infants receiving cow's milk (table 5). It is only slightly higher than the value of 4.94 which was found for the premature infants in group 2 receiving diets of cow's milk of relatively low protein content. Significantly lower is the coefficient of 4.22 found in premature infants receiving human

12. Daniels, A. L., and Hejinian, L. M.: Growth of Infants from the Standpoint of Physical Measurements and of Nitrogen Metabolism, Am. J. Dis. Child. **38**:499 (Sept.) 1929.

13. Rougichitch, O. S.: The Day and Night Creatinine and Creatine in the Urine of Infants, Arch. Dis. Childhood **1**:289, 1926; Uric Acid and Creatinine in the Urine of Infants, Am. J. Dis. Child. **31**:504 (April) 1926.

14. Catherwood, R., and Stearns, G.: Creatine and Creatinine Excretion in Infancy, J. Biol. Chem. **119**:201, 1937.

milk.[15] A rise in creatinine excretion after change from human to cow's milk occurred in 9 of the 12 infants who were studied on both types of diet. It is of interest to note that when the increase did occur it began immediately and had reached the higher level within four to five days (table 6). In several instances (E. H., W. D. and L. F.) in which human milk was used after a period of cow's milk feeding, there was a prompt decrease in creatinine excretion (chart).

The Excretion of Creatine.—The data on creatine excretion shown in table 1 confirm the report of Paffrath and Ohm[1] that premature infants receiving human milk excrete little or no creatine. The creatine coefficients ranged from 0 to 2.6 for individual days, and the average for the entire series was 0.40 mg. of nitrogen per kilogram per day, or 10 per cent of the total creatinine excretion. In only one instance was the average creatine coefficient greater than 1.0 (W. D.).

TABLE 6.—*Excretion of Creatinine After Change to Diet of Relatively High Protein Content*

Type of Diet	No. of Observations	No. of Infants	Nitrogen Intake, Mg. per Kg.	Creatinine Coefficient
Premature Infants:				
Human milk	102	15	383	4.22
One day on cow's milk	4	4	844	4.50
Two to three days on cow's milk	13	9	844	4.67
Four to five days on cow's milk	22	16	856	5.07
Full term Infants:				
Cow's milk	92	13	831	5.04

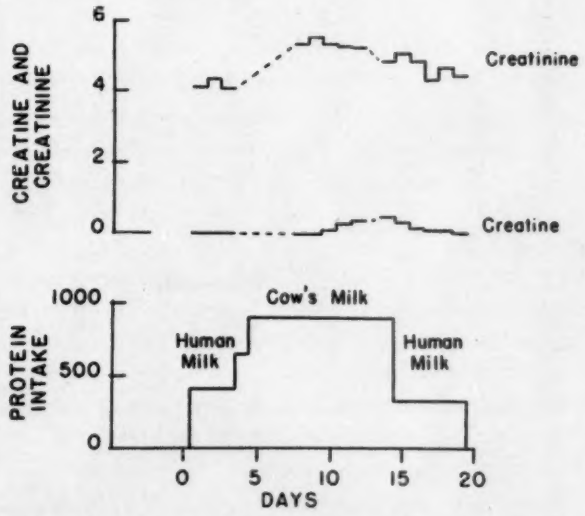
The nitrogen intake of these premature infants (2.4 Gm. of protein per kilogram per day) was much lower than that fed to full term infants (table 4). Since creatinuria has been shown to be influenced by the nitrogen intake,[16] premature infants receiving higher protein intakes were studied, in order to compare them with full term infants. The results of four hundred and thirty-six days of observation on 35 premature infants after a preliminary period of constant diet of at least three days before the onset of observations are presented in table 3. The pronounced variations between individual infants are at once apparent.

15. The difference in the excretion of creatinine on the two types of diet cannot be attributed to an increased ingestion of creatinine, since the cow's milk diets contained slightly less creatinine (0.65 mg.) than the human milk diets (0.88 mg.), according to the data given by Denis and Minot (Denis, W., and Minot, A. S.: The Non-Protein Nitrogenous Constituents of Cow's Milk, J. Biol. Chem. **38**:453, 1919; Methods for the Quantitative Determination of the Nitrogenous Constituents of Milk, ibid. **37**:353, 1919) for the creatinine content of the two types of milk (table 5).

16. Footnotes 10 and 11.

Table 7 presents the data arranged according to the length of time the infants had been receiving cow's milk formulas and shows that there is a gradual increase in excretion of creatine following continued feeding of diets of cow's milk. The change was most pronounced in the infants receiving relatively high protein diets (over 700 mg. of nitrogen per kilogram); hence by the third week of these diets, the average creatine coefficients for this group were the same as for young full term infants.[17] Infants receiving cow's milk diets of relatively low protein content show a slower rise in creatinuria.

There were great individual variations in the rate at which creatinuria increased after change to a high protein diet. Of the 35 pre-



Effect of alterations in protein intake on creatine and creatinine excretion (infant E. H.). Figures represent milligrams of nitrogen per kilogram per twenty-four hours.

mature infants receiving more than 700 mg. of nitrogen per kilogram, 9, or 26 per cent, never excreted as much as 1 mg. of creatine nitrogen

17. It should be noted that the average creatine coefficient (1.93) found for young full term infants differs from those reported in the literature: 5.68 (Rougichitch[13]), 3.71 (Daniels and Hejinian[12]), 3.89 (Marples and Levine[2]) and 3.9 (Catherwood and Stearns[14]). This may be due to the lower age of the group of infants studied here. Catherwood and Stearns[14] found that the average creatine coefficient rose gradually from 1.71 during the first week of life to a level of 3.9, which was attained between the fifteenth and twentieth weeks of life. Our full term infants ranged from 18 to 85 days of age; the average age was 43 days. The coefficient of correlation between age and creatine excretion was 0.565 for this group, as compared with the coefficient of 0.731 found by Catherwood and Stearns[14] for infants ranging from birth to 1 year of age.

per kilogram during the seven to eighteen days after the change of diet during which they were studied. However, they do not differ from young full term infants in this respect, since 2 of the latter group of 13

TABLE 7.—*Urinary Excretion of Creatine and Creatinine by Premature and Full Term Infants Receiving Cow's Milk*

Length Time on Cows Milk, Days	No. of Infants	No. of Days of Observation	Average Intake, Mg. per Kg. per 24 Hours: Total Nitrogen	Creatinine Nitrogen	Creatine Nitrogen	Urinary Output, Mg. per Kg. per 24 Hours: Total Nitrogen	Creatinine Nitrogen	Creatine Nitrogen	Average per Cent of Nitrogen Intake Excreted in Urine
Premature Infants with Nitrogen Intake Less Than 700 Mg./Kg./Day									
1- 7	6	18	557	0.71	0.43	115	4.63	0.32	20.6
8-14	5	12	588	0.75	0.45	190	4.64	0.37	32.3
15-21	4	18	610	0.77	0.47	287	5.46	1.48	46.4
22-28	3	11	592	0.75	0.46	278	4.84	1.01	46.9
Premature Infants with Nitrogen Intake More Than 700 Mg./Kg./Day									
1- 7	20	69	857	1.09	0.66	316	4.96	0.74	36.9
8-14	23	75	855	1.09	0.66	415	5.08	1.42	48.5
15-21	16	73	898	1.14	0.69	497	5.13	2.62	55.3
22-28	14	60	880	1.12	0.68	496	5.41	2.22	56.4
29-35	17	54	885	1.12	0.68	497	5.34	2.11	56.2
36-42	8	44	862	1.09	0.66	477	5.31	1.84	55.4
43-49	7	33	865	1.10	0.67	533	5.21	1.84	61.6
Young Full Term Infants									
15-21	3	6	867	1.10	0.67	462	4.99	1.79	53.3
22-28	4	11	862	1.09	0.66	441	4.91	1.41	51.2
29-35	3	7	872	1.11	0.67	489	4.72	1.15	56.6
36-42	5	14	833	1.06	0.64	523	5.02	1.43	62.5
43-49	4	11	905	1.15	0.70	573	4.96	1.72	63.4

TABLE 8.—*Coefficients of Correlation Between Creatine and per Cent of Nitrogen Intake Excreted in Urine*

Subject	Range of Nitrogen Intake, Mg. per Kg.	Range of Urinary Nitrogen, Mg. per Kg.	Range of per Cent of Nitrogen Intake in Urine	Range of Creatine Coefficient	Coefficient of Correlation Between per Cent of Nitrogen Intake in Urine and Creatine	No. of Observations
R. S.	377-737	79-334	24.0-46.3	0.22-2.38	0.9573	6
S. P.	366-852	66-490	13.5-60.0	0.00-1.48	0.8841	10
P. J. A.	752-927	160-513	21.3-63.0	0.20-3.97	0.8791	17
F. Z.	379-1066	81-452	19.4-45.1	0.00-0.73	0.8742	11
J. G.	807-909	257-412	29.6-48.7	0.00-1.69	0.8734	9
W. J.	557-634	129-269	20.3-48.3	0.00-2.37	0.8503	13
H. C. A.	781-931	179-506	22.1-63.2	0.00-3.88	0.8208	17
J. S.	698-738	343-431	48.0-61.7	0.72-1.13	0.8140	5
W. D.	438-948	89-437	14.6-48.2	0.41-2.76	0.8127	14
J. C.	385-899	103-661	24.3-79.4	0.00-2.00	0.8030	37
R. E. S.	779-910	333-520	41.4-57.2	0.00-1.80	0.7747	6
E. H.	265-902	80-426	25.3-48.7	0.00-4.39	0.7135	12
E. P.	432-770	74-251	16.0-35.1	0.29-1.43	0.6860	10
M. P.	845-898	424-514	47.5-59.1	0.32-2.02	0.6290	7

also failed to show a creatine coefficient as high as 1 during the twenty-three to thirty-two days they were studied after the change of diet. It seems probable that the creatine metabolism of young infants, both premature and full term, differs from that of older full term infants.

Such differences with respect to nitrogen retention [18] and urea clearance tests [19] have been demonstrated by Gordon and his co-workers.

Another interesting facet of the problem is revealed in table 7, i. e., that the greater the percentage of the nitrogen intake excreted in the urine, the greater is the creatinuria. The coefficient of correlation calculated for the entire series of observations (701 in all) was 0.59 ± 0.02. However, coefficients calculated individually for those infants who were studied during the first three weeks after the change of diet, the period when creatinuria was increasing, showed a higher degree of correlation (0.63 to 0.96) (table 8). The coefficient of correlation between the total nitrogen excreted in urine and the creatine excretion was 0.58 ± 0.02 for the entire series.

COMMENT

Creatinine.—The creatinine excretion of premature infants receiving cow's milk does not differ significantly from that of full term infants receiving similar diets. The average coefficients were 5.09 (range 4.06 to 6.48) for premature infants and 5.04 (range 4.62 to 5.48) for full term infants. Even when the protein intake is as low as 3.1 Gm. per kilogram per day, the creatinine coefficient is not significantly lower (4.94). However, premature infants receiving human milk, with an average protein intake of 2.4 Gm. per kilogram, excrete significantly less creatinine. It has been claimed [20] that excretion of creatinine is not related to nitrogen metabolism. However, it seems probable that in this specific instance (i. e., the abrupt increase in creatinine excretion following the change from human milk, with its low protein content, to cow's milk, with a higher protein content) the excretion of creatinine is definitely related to the intake of nitrogen. This conclusion is further strengthened by the observation that for 2 of the infants fed human milk after a period of cow's milk feeding the creatinine coefficients decreased. There was no significant difference in the creatinine intake on the two types of diet.

Catherwood and Stearns [14] have reported that full term infants receiving human milk for the first two weeks of life excreted relatively less creatinine than subsequently when they were fed cow's milk diets. They found a gradual increase in the creatinine coefficient with increasing age but make no note of any abrupt increase following the change in diet such as we observed in premature infants. It does not seem

18. Czerny, A., and Keller, A.: Des Kindes Ernährung, Ernährungsstörungen und Ernährungstherapie, Vienna, Franz Deuticke, 1925, vol. 1, p. 693, table 693. Gordon, Levine, Wheatley and Marples.[3]

19. Gordon, H. H.; Harrison, H. E., and McNamara, H.: The Urea Clearance of Young Premature and Full Term Infants, J. Clin. Investigation **21**:499, 1942.

20. Footnotes 10 and 14.

likely that age played an important part in the increase observed in premature infants, since the infants ranged from 1 to 68 days of age when changed to cow's milk. An analysis of the data failed to reveal any upward trend of creatinine excretion with increasing age of the infant during the narrow age range studied here.

Creatine.—The data presented here do not support the concept that there is a fundamental difference in creatine metabolism between premature and young full term infants provided that diets of relatively high protein content are ingested by both groups. It is true, as Paffrath and Ohm [1] reported, that premature infants receiving human milk excrete little or no creatine whereas young full term infants always exhibit some creatinuria.[14] The fact that creatinuria does occur in the majority of the premature infants at some subsequent time after the ingestion of diets of relatively high protein content would indicate that the difference lies, perhaps, in a relatively greater anabolic requirement of creatine or its precursors on the part of the more rapidly growing premature organism rather than in any basic aberration of creatine metabolism.

Catherwood and Stearns [14] concluded from extensive studies of normal infants that the excretion of creatine bears no relation to any phase of nitrogen metabolism. However, during relatively short periods (i. e., up to three weeks after change to a diet of relatively high protein content) there does appear to be a definite correlation between creatinuria and nitrogen excretion in the urine, which might imply an inverse relationship between creatinuria and nitrogen retention.

SUMMARY

Premature infants receiving a relatively low protein diet of human milk excreted significantly smaller amounts of creatinine (4.22 mg. of creatinine nitrogen per kilogram per twenty-four hours) than did premature infants receiving formulas of cow's milk (5.09 mg. of creatinine nitrogen per kilogram per twenty-four hours). When the infants were changed to the latter diet, the creatinine coefficients promptly rose to the usual level of infancy and childhood and were maintained at that level.

The creatine excretion of both premature and young full term infants of comparable ages was variable.

Premature infants receiving human milk, with an average protein intake of 2.4 Gm. per kilogram per day, excreted little or no creatine in the urine.

Premature infants receiving cow's milk, with an average protein intake of 3.1 Gm. per kilogram per day, also had little or no creatinuria.

When the protein intake was increased to an average of 5.2 Gm. per kilogram per day, there was a gradual increase in creatinuria, so that during the third week on such a diet the average creatine coeffi-

cient of premature infants was not significantly different from that of young full term infants of comparable ages receiving similar diets. The creatine coefficients of the latter group ranged from 0.44 to 3.69 mg. of creatine nitrogen per kilogram per twenty-four hours, with an average of 1.93.

There were wide variations between individual infants in the length of time after change in diet before creatinuria appeared and also in the level of creatinuria when a relatively constant rate of excretion had been reached.

Creatinuria appears to be related to nitrogen metabolism, at least during the first three weeks after the change of diet from relatively low to relatively high protein intake. For 14 infants studied during this period the coefficients of correlation between excretion of creatine and percentage of ingested nitrogen excreted in the urine ranged from 0.95 to 0.62.

525 East Sixty-Eighth Street.

ATTEMPTS TO PRODUCE ABSORPTION OF POLIOMYELITIS VIRUS BY PERIPHERAL NERVES IN VITRO

JOHN A. TOOMEY, M.D.

LINDA A. TISCHER, M.D.
AND
WILLIAM S. TAKACS, B.S.
CLEVELAND

In preliminary experiments, peripheral nerves of rachitic animals were ground with purified eluted poliomyelitis virus. The supernatant fluid was found to be noninfectious, while the centrifugate produced the disease. When well medullated nonrachitic peripheral nerve fibers were ground with eluted virus, the supernatant fluid was found to be infectious and the centrifugate noninfectious. The evidence was interesting though not conclusive, since so few animals were used in each experiment that chance might explain the results. However, the lead was important enough to follow; if the conclusion could be confirmed it might then be inferred that the disease would be contracted if the medullated fibers of peripheral nerves were disturbed in some manner. Plans were made to repeat these experiments with a sufficient number of animals to make the results conclusive.

The objective was to determine whether there is any difference between the absorptive power of rachitic and that of nonrachitic peripheral nerves added to and ground with purified eluted virus.

EXPERIMENTAL PROCEDURE

Material.—The virus used in the following experiments was a 10 per cent suspension of eluted Flexner M. V. strain (obtained from Dr. A. B. Sabin), the method of purification and elution being that previously described.[1] Macaca mulatta monkeys were used as the test animals.

The rachitic animals used in our previous experiment were baby monkeys obtained immediately after weaning. Their blood serum had low concentrations of phosphorus (under 1.5 mg. per hundred cubic centimeters) and calcium (under 6.2 mg. per

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From the Division of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University.

1. Sabin, A. B.: Experiments on the Purification and Concentration of the Virus of Poliomyelitis, J. Exper. Med. **56**:307 (Sept.) 1932. Schaeffer, M., and Brebner, W. B.: Purification of Poliomyelitic Virus, Arch. Path. **15**:221 (Feb.) 1933.

hundred cubic centimeters). We were unable to obtain enough newly weaned animals for these experiments. The infant monkeys that were delivered to us died in a few months, after a futile attempt to make them sufficiently rachitic. Their deaths were due to various causes, such as tuberculosis, parasitosis and worms. The experiment lagged several months, until finally we were able to obtain 10 animals with severe deformities due to fully developed and severe rickets, animals that had normal calcium and abnormally low phosphorus levels in their blood serums and the bony signs of rickets by roentgen examination. Rickets had been produced in these monkeys by feeding them a rickets-producing diet over a period of months in another laboratory.[2]

A second group, of nonrachitic monkeys, were daily fed a diet of apples, bananas, carrots, cooked white rice, white bread soaked in cold whole milk, ½ teaspoonful of a preparation of wheat germ (Embo) and 5 drops of carotene in oil. Two drops of viosterol in oil was given twice weekly. In direct contrast to the rachitic monkeys, these looked healthy and active; the fur remained sleek, and they did not seem to have the gastroenteritis that troubled so many of our own laboratory animals.

A third group also was composed of normal, healthy animals. They were given the same nonrachitogenic diet as was given to the second group, but without the wheat germ, carotene and viosterol. These monkeys were used to demonstrate the fact that the virus dilutions were virulent.

Calcium and phosphorus determinations were made on the blood serum of every rachitic and nonrachitic animal before it was operated on or inoculated.

It took the greater part of a year to get these animals ready for the experiment. After the preliminary preparations were completed and the animals were ready to be operated on, the experiment proceeded as will be outlined.

Method.—With the animal under general anesthesia and with sterile operative technic, a portion of the right sciatic nerve peripheral to the notch was obtained. The specimen removed weighed from 0.28 to 0.50 Gm., depending on the size of the animal; usually it approximated 0.35 Gm. It was divided into two parts, of which one was placed in solution of formaldehyde U. S. P. diluted 1 to 10 for microscopic and polariscopic studies and the other was saved for in vitro experiments. The results of the latter experiments only are considered in this report.

The specimens of rachitic and of nonrachitic nerves were washed four times with physiologic solution of sodium chloride to remove adherent blood and then carefully weighed on a microbalance. Each specimen was placed in 0.1 Gm. of ground glass and ground for about ten to fifteen minutes, until a smooth paste resulted. Enough of a 10 per cent suspension of eluted virus was added to this paste to make a 5 per cent nerve suspension. The nerve-virus mixture was then put into a glass container holding exactly 100 glass beads and ground in a ball mill for eighteen hours. At the end of this time, the supernatant fluid was decanted into a tube and was centrifuged for ten minutes at 4,000 revolutions per minute. The resulting supernatant fluid was decanted off and used for animal inoculations. The centrifugate was suspended in 3 to 5 cc. of physiologic solution of sodium chloride, shaken and centrifuged for ten minutes at 4,000 revolutions per minute; the resulting supernatant fluid was discarded. The centrifugate underwent two more washings; in the last washing it was resuspended in physiologic solution of sodium chloride and brought to the original volume. An angle centrifuge was used throughout.

2. Laboratory of the Babies and Childrens Hospital, Henry J. Gerstenberger, M.D., Cleveland.

For control purposes, an equal volume of a 5 per cent suspension of eluted virus was put into a glass flask containing 100 glass beads and treated exactly as was the other specimen described. After eighteen hours, the eluted virus became turbid and gritty, probably because of minute particles of ground glass. The control virus was centrifuged and separated into the control supernatant fluid and centrifugate. All fluids, whether they were combinations of supernatant fluids or centrifugates of rachtic, nonrachitic or control specimens, were centrifuged at the same time, in the same type of holder, in the same machine and at the same speed.

Immediately after preparation, the supernatant fluids and the centrifugates were individually injected into M. mulatta monkeys. The dose was always 0.1 cc. injected intracerebrally. After the inoculation, the animals were observed for signs of poliomyelitis and killed at the onset of complete paralysis. They were examined completely post mortem, and the specimens removed were fixed in a 10 per cent concentration of solution of formaldehyde U. S. P. and stained routinely with

TABLE 1.—*Blood Calcium and Phosphorus Levels of Rachitic and of Nonrachitic Monkeys*

Condition of Monkey	Animal	Date	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.
Rachitic	2706	10/14/41	9.0	1.5
	2715	10/14/41	9.4	1.2
	2721	10/14/41	9.4	1.1
	2728	10/14/41	9.3	1.4
	2736	10/14/41	9.2	1.3
	2750	11/13/41	11.2	2.6
	2757	11/13/41	11.2	1.9
	2762	11/13/41	10.9	1.8
	2771	11/13/41	9.9	1.4
	2778	11/13/41	10.3	1.0
Nonrachitic	2705	10/15/41	10.5	5.0
	2708	10/17/41	10.3	5.0
	2714	10/17/41	9.9	5.1
	2722	10/18/41	9.8	7.1
	2729	10/20/41	9.0	5.1
	2832	2/ 2/41	9.4	4.5
	2833	2/24/42	10.7	4.5
	2840	3/ 4/42	10.5	5.1

hematoxylin and eosin and Nissl stains. The sections were also studied polariscopically.

The blood calcium and phosphorus values obtained on the day of operation are listed in table 1.

For convenience, it will be assumed that "rachitic supernatant fluid" refers to the ground rachitic nerve plus virus supernatant fluid; "nonrachitic supernatant fluid," to ground nonrachitic nerve plus virus supernatant fluid; "rachitic centrifugate," to rachitic nerve plus virus centrifugate; "nonrachitic centrifugate," to nonrachitic nerve plus virus centrifugate, and "control supernatant fluid" and "control centrifugate," to control virus-containing supernatant fluid and centrifugate, respectively.

RESULTS

The results are outlined in table 2. The reactions obtained in the animals were varied. They ranged from mere anorexia to complete

TABLE 2.—*Variations in Severity of Clinical Symptoms*

Groups of Macaca Mulatta Monkeys Injected With	Group 1 Questionable and Mild Disease					Group 2 Severe Disease			
				Total				Total	
	*	†	‡	No.	%	§	Q	No.	%
Rachitic nerve plus virus supernatant fluid (15)‖..	1	4	3	8	53	0	6	6	40
Nonrachitic nerve plus virus supernatant fluid (10)	0	1	1	2	20	1	7	8	80
Control virus supernatant fluid (13).....	1	1	2	4	31	3	6	9	69
Rachitic nerve plus virus centrifugate (15).....	0	5	5	10	67	1	4	5	33
Nonrachitic nerve plus virus centrifugate (10).....	0	2	2	4	40	1	5	6	60
Control virus centrifugate (13).....	2	1	6	9	69	0	4	4	31

* General symptoms: anorexia, furring, red face.
† Questionable or minimal weakness of extremities.
‡ Some weakness of extremities.
§ Paralysis of 1 to 3 extremities.
Q Quadriplegia, complete paralysis.
‖ One animal out of 15 died of causes other than poliomyelitis.

TABLE 3.—*Reactions in Inoculated Animals*

Supernatant Fluid

Rachitic				Nonrachitic				Control			
	Postinoculation, Days				Postinoculation, Days				Postinoculation, Days		
Monkey	Symptoms	Quadriplegia	Autopsy	Monkey	Symptoms	Quadriplegia	Autopsy	Monkey	Symptoms	Quadriplegia	Autopsy
2709	1	No	2	2710	8	No	10	2705	..	...	6
2716	5	No	None	2717	..	9	9	2708	5	7	7
2723	11	No	None	2724	13	No	None	2714	6	No	7
2731	6	No	7	2732	7	No	None	2722	7	No	None
2737	9	No	12	2738	4	12	12	2729	5	9	9
2751	5	No	7	2835	5	7	8	2755	7	No	None
2752	5	7	7	2836	5	6	8	2706	5	No	10
2758	5	No	14	2841	4	6	6	2767	4	No	6
2759	5	12	12	2842	4	6	8	2776	4	8	8
2763	4	No	9	2846	4	6	6	2783	3	No	5
2764	4	No	14					2832	5	6	8
2772	3	4	5					2833	4	7	8
2773	2	4	5					2840	3	5	6
2779	3	6	6								
2780	3	5	5								

Centrifugate

Rachitic				Nonrachitic				Control			
	Postinoculation, Days				Postinoculation, Days				Postinoculation, Days		
Monkey	Symptoms	Quadriplegia	Autopsy	Monkey	Symptoms	Quadriplegia	Autopsy	Monkey	Symptoms	Quadriplegia	Autopsy
2711	11	No	None	2712	7	8	8	2713	14	No	37
2718	23	32	32	2719	12	No	None	2715	5	No	None
2725	11	No	None	2726	22	No	None	2720	..	7	7
2733	7	No	None	2734	7	No	11	2727	8	13	13
2739	9	No	None	2740	4	No	8	2735	7	8	8
2753	5	No	None	2837	5	No	34	2741	5	No	None
2754	5	No	None	2838	5	14	16	2756	5	No	None
2760	5	No	None	2843	5	11	13	2768	4	No	27
2761	3	No	19	2844	5	7	8	2777	4	No	29
2765	4	No	None	2847	4	13	14	2784	4	No	None
2766	4	No	None					2839	6	No	None
2774	4	5	6					2845	5	8	8
2775	5	9	9					2848	3	No	None
2781	3	9	9								
2782	3	..	6								

quadriplegia. The animals were grouped according to the objective response, i. e. according to the severity of the disease. Thus, in the table the questionable or minimally weak animals and the severely paralyzed ones were designated as groups 1 and 2, respectively.

In group 2, the "nonrachitic supernatant fluid" gave an 80 per cent reaction rate. This might seem significant until it is noted that the "control supernatant fluid" produced nearly a 70 per cent rate. There did not seem to be any absorption by these nerves.

The "rachitic supernatant fluid" gave a 40 per cent reaction rate. The "rachitic centrifugate" gave a 33 per cent rate in group 2, as compared with 31 per cent in the control group and 60 per cent in the comparable nonrachitic group.

If only quadriplegia is considered, it can be seen that the nonrachitic supernatant fluid was the most virulent of all the substances. Whether this indicates a lack of absorption of the virus by this type of nerve is unknown. Nothing definite can be said, however, since the results were so equivocal that a few more positive or negative results either way would nearly equalize the percentages.

COMMENT

The results of this experiment must be considered negative; they do not bear out our original experience.

There is a point which may or may not be of importance but which should be mentioned. Our previous experiments were done with newly weaned animals, and they were started as soon as rickets was produced. The present experiments were done on animals the chronologic age of which was at least three times as great as that of the weaned animals used previously, or approximately 3½ years, animals that had passed through several attacks of rickets. Even though the phosphorus level was low and the roentgenograms revealed changes typical of rickets, there may have been some condition created in the peripheral nerves different from that in the young animals previously used.

The present experiment was further complicated by an epidemic of dysentery which infected 12 animals; by intestinal and pulmonary parasitosis in 7; by tuberculosis of the lung and spleen in 3; by anemia of unknown origin in 1; by subcutaneous edema of the right side of the face in 1, and by pneumonia in 1. These conditions, however, did not seem to militate against the experiments, because the animals contracted poliomyelitis long before the clinical conditions mentioned as complicating factors were recognized. In the 3 instances in which tuberculosis was present, there was a loss of weight; the animals did not look well clinically, and there was a suspicion of some chronic infection, but a

positive diagnosis had not been made prior to death. The fact that tuberculosis was present, however, did not interfere with the experiments and would not change the results.

CONCLUSION

There did not seem to be any difference between the absorptive power of peripheral nerves of nonrachitic and of rachitic M. mulatta monkeys (3½ year old animals) when ground with purified eluted poliomyelitis virus.

3395 Scranton Road.

POSSIBILITY OF ARTIFICIAL SENSITIZATION TO TUBERCULIN

MILTON I. LEVINE, M.D.
AND
MARGARET F. SACKETT, R.N.
NEW YORK

Controversy still exists regarding the possibility of artificial sensitization to tuberculin as the result of repeated tuberculin tests. The literature on this subject, which has been reviewed by Aronson and Nicholas [1] and Nelson, Mitchell and Brown,[2] shows a variance of opinion and a lack of uniformity in the results.

If the reaction to tuberculin is regarded as an allergic response due to the interaction of antigen and antibody [3] and if the thesis is accepted that absorption into the system of an adequate amount of specific protein produces an active sensitization to that protein,[4] it would be reasonable to expect the development of a specific sensitivity of the tissues after repeated intradermal or subcutaneous injections of sufficiently large amounts of tuberculin. Aronson and Nicholas,[1] Steele and Willis [5] and Reichle and Goldblatt [6] reported the development of sensitization after repeated cutaneous tests with the usual doses of tuberculin or tuberculoprotein. The first authors [1] noted that the reactions to this artificial

From the Bureau of Laboratories, Department of Health, and the Department of Pediatrics, Cornell University Medical College.

1. Aronson, J. D., and Nicholas, R. V.: Comparative Value of Tuberculoprotein and Old Tuberculin, with Special Reference to Sensitization, J. Immunol. **25**:483, 1933.

2. Nelson, W. E.; Mitchell, A. G., and Brown, E. W.: The Possibility of Sensitization to Tuberculin, Am. Rev. Tuberc. **37**:286, 1938.

3. Topley, W. W. C., and Wilson, G. S.: Principles of Bacteriology and Immunology, ed. 2, Baltimore, William Wood & Company, 1937, p. 909. Gay, F. P., and others: Agents of Disease and Host Resistance, Springfield, Ill., Charles C. Thomas, Publisher, 1935, p. 1006. Kolmer, J. A.: Infection, Immunity and Biologic Therapy, ed. 3, Philadelphia, W. B. Saunders Company, 1923, p. 1056.

4. Zinsser, H.; Enders, J. F., and Fothergill, L. D.: Immunity, New York, The Macmillan Company, 1939, p. 344. Ratner, B.: Allergy in Childhood, J. Pediat. **12**:730, 1938.

5. Steele, A. H., and Willis, H. S.: Study of the Increase of Sensitiveness in Normal Children Produced by Repeated Injections of Tuberculin, Nat. Tuberc. A. Tr. **30**:120, 1934.

6. Reichle, H. S., and Goldblatt, H.: Sensitization of Guinea Pigs and Production of Allergy and Anaphylaxis to Tuberculoprotein, Am. Rev. Tuberc. **27**:291, 1933.

sensitization reached their maximum redness and infiltration in twenty-four hours rather than the usual forty-eight.

On the other hand, Nelson, Mitchell and Brown [2] concluded their article on repeated tuberculin tests with old tuberculin and purified protein derivative with the following statement:

> . . . there appears to be no evidence that tuberculin sensitization is induced by tuberculin injections in man. This does not imply that sensitization to tuberculin or tuberculoprotein is impossible, but does indicate that such sensitization will probably not occur from the ordinary use of tuberculin for skin testing purposes.

Barnwell and Pollard [7] were also unable to induce sensitization by repeated injections of old tuberculin or tuberculoprotein in newborn babies. They suggested, however, that infants are probably more difficult to sensitize than adults, as already indicated by the findings of Freund.[8] Siebert [9] reported that a preparation of old tuberculin had little or no sensitizing effect, and later [10] she demonstrated that the poor antigenicity of old tuberculin is due to the fact that its protein is of low molecular weight.

In view of this variance of opinion, the results obtained for a group of infants and children who were repeatedly tested with relatively large amounts of freshly prepared old tuberculin are reported. To our knowledge, studies following the inoculation of unusually large amounts of tuberculin have not thus far been recorded.

EXPERIMENTAL MATERIALS AND METHODS

The data were accumulated during the course of an investigation on the efficacy of BCG in immunization against tuberculosis. This study has been carried on during the past fifteen years in the city of New York by the Bureau of Laboratories of the Department of Health. During the course of the investigation over 1,000 children were inoculated with BCG vaccine and an approximately equal number were held as controls. The children were referred to the Bureau of Laboratories from tuberculosis clinics and hospitals in the city of New York. All were originally from tuberculous homes and were followed during and after the first year of life. Many of the children were hospitalized, and others were brought weekly or several times monthly to the clinics; thus an opportunity for frequent tuberculin tests was afforded.

The routine dose of tuberculin used for intradermal testing was 0.1 mg.; in many instances this dose was raised to 1 and 10 mg., and in a few instances to as high as 100 mg. Reactions in the children who were hospitalized were read

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7. Barnwell, J. B., and Pollard, H. M.: Comparison of Old Tuberculin with Tuberculin Protein T. P. T., Am. Rev. Tuberc. **30**:482, 1934.

8. Freund, J.: Influence of Age on Antibody Formation, J. Immunol. **18**:315, 1930.

9. Siebert, F. B.: Chemical Composition of Active Principle of Tuberculin: Local Cutaneous Sensitization (Arthus' Phenomenon) Produced in Normal Rabbits and Guinea Pigs by Protein of Tuberculin, J. Infect. Dis. **51**:383, 1932.

10. Siebert, F. B.: Relationship Between the Sensitizing Properties of Tuberculo-Protein and Its Molecular Weight, Nat. Tuberc. A. Tr. **29**:1-7. 1933.

and measured at the end of forty-eight hours by pediatricians; the results of the tests performed at the clinics were read forty-eight hours later by specially trained nurses. A reaction was considered negative if at the end of forty-eight hours there was no edema or redness. When the edema was 5 to 10 mm. in diameter, the reaction was reported as ±. An edematous reaction of over 10 mm. in diameter was considered positive. All tests were performed on the left forearm of the child. This afforded an added opportunity for the study of possible local sensitization.

The 62 children reported on in this paper were selected from the control group because of the frequency of tuberculin tests with varying doses. The number of tests varied from 3 to 61 during periods of one to five years of observation, and doses of tuberculin ranged from 0.1 to 100 mg.

In view of the fact that children who have been exposed to tuberculous persons may easily have acquired a sensitivity from absorption of tubercle bacilli, only children with no known exposure were selected for this study. The distribution of subjects is shown in table 1.

TABLE 1.—*Distribution of Subjects and Tests*

Number of Subjects	Number of Tuberculin Tests	Number of Subjects	Number of Tuberculin Tests
1	61	4	13
1	46	1	12
1	45	1	11
1	40	1	10
1	37	1	9
1	34	5	8
1	29	1	7
1	27	5	6
1	24	3	5
2	23	17	4
2	16	9	3
1	14		

Valid interpretation of the results must give consideration to the following questions: Can sensitization be induced in human beings by the usual routine tuberculin tests given with more than usual frequency? Do larger doses of tuberculin increase the possibility of sensitization? Does the interval between tests influence sensitization, or does frequency of testing build up a resistance to sensitization? Is age a factor in the development of sensitization? Does local sensitization of the tissues result from repeated tuberculin tests in the same area?

RESULTS

A study of the results of frequent inoculations of tuberculin in the 62 subjects reported on in this paper reveals that all except 5 children continued to give negative reactions to the tests.

Table 2, presenting the results for the 22 subjects most frequently tested, includes the 5 children just mentioned.

It is evident from a review of these results that a more detailed study is needed of the few children in whom the reaction to tuberculin became positive (subjects 9, 11, 16, 19 and 21).

CASE 9.

Reaction to tuberculin	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	+	+
Age in months	1	1	1	2	2	2	2	3	3	3	3	4	4	4	4	4	5	5	5	5	6	6	14	38			

This child was born at Sea View Hospital and was separated at once from his mother, who had active tuberculosis. He remained at Sea View Hospital in a special ward for normal babies for the first six months; then he was sent to the New York Foundling Hospital and later to a foster home. Roentgenograms taken

TABLE 2.—*Results of Frequent Tuberculin Tests*

Subject Number	Age Period During Which Tests Were Performed, Months	Total Tests	Number of Tests During Period of Most Frequent Testing	Reactions to Tests
1	1-15	61	61 in 15 months	Negative
2	1-60	46	45 in 19 months	Negative
3	3-47	45	44 in 21 months	Negative
4	1-14	40	40 in 14 months	Negative
5	1-51	37	36 in 10 months	Negative
6	1- 9	34	34 in 9 months	Negative
7	1-10	29	29 in 10 months	Negative
8	1- 7	27	27 in 7 months	Negative
9	1-38	24	22 in 6 months	All negative except + at 14th and 38th month
10	1- 7	23	23 in 7 months	Negative
11	1- 7	23	23 in 7 months	Last 2 tests +; died of tuberculosis
12	1- 4	16	16 in 4 months	Negative
13	1-45	14	11 in 5 months	Last test ±
14	6-57	13	12 in 22 months	One test at 22 mo. +; all others negative
15	2- 6	13	13 in 6 months	Negative
16	7-52	13	10 in 31 months	4th test, 21 mo., ++; 8th test, 27 mo., ±; 10th test, 35 mo., ++; 13th test, 52 mo., +
17	2-55	12	Scattered	Negative
18	12-52	11	Scattered	Negative
19	1-14	10	9 in 6 months	14th month, +
20	6-58	9	Scattered	Negative
21	7-67	16	Scattered	6th test, 19 mo., ±; 7th test (10 mg.), 21 mo., +; all others negative
22	1- 6	13	13 in 6 months	Negative

at the Foundling Hospital when he was 14 months old showed moderate mediastinal widening. A subsequent plate, taken at the age of 38 months, showed beginning calcification in the upper lobe of the left lung and in the left hilar region. Later roentgenograms showed the development of pronounced calcification in these areas.

CASE 11.

Reaction to tuberculin	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	+	+
Age in months	1	1	2	2	3	3	3	3	4	4	4	4	5	5	5	5	6	6	6	6	7	7	7				

This child was born at Sea View Hospital of a mother with far advanced tuberculosis. She was separated from her mother at birth and placed in the well baby ward. She was in excellent condition until 5 months of age, when a low

grade fever developed. This fever was interpreted as due to an infection of the upper respiratory tract. Mantoux tests and roentgenograms at this time revealed no evidence of tuberculosis. When she was 6 months of age a massive enlargement of the right hilar nodes developed, although the reaction to tuberculin was still negative. At 7 months the Mantoux reaction became positive and the enlargement of the right hilar nodes more pronounced. The tuberculous process was rapidly progressive, and the child died at 14 months of tuberculous bronchopneumonia.

CASE 16.

Reaction to tuberculin	—	—	—	+	+	—	—1	—	—	—	+	+	—	—	+
Age in months	7	7	11	21	24	24	24	27	32	35	42	48	52	

This child was never exposed to tuberculosis, since an early diagnosis of tuberculosis in her brother was found to be incorrect. When she was 1 year of age bronchopneumonia developed, from which she made an uneventful recovery. She was in the hospital and in convalescent homes from 11 to 14 months of age. At 21 months a tuberculin test elicited a positive reaction. At 23 months the child was readmitted to Babies Hospital with lobar pneumonia, remaining there for three weeks. Three weeks later a recurrence of pneumonia led to her admission to Bellevue Hospital (age 24 months). After her discharge she remained home and was followed in the clinic. Roentgenograms taken when she was 27 months old showed only increased hilar markings.

CASE 19.

Reaction to tuberculin	—	—	—	—	—	—	—	—	—	+++
Age in months	1	1	1	1	2	2	2	2	6	14

This child was born of a tuberculous mother at Sea View Hospital and was removed immediately to the well baby ward, where he remained until 2½ months of age. He was then cared for at a foster home. When he was 14 months of age, the reaction to a tuberculin test was read as 3 plus. Roentgenograms taken at 21 months showed early calcification of the right hilar nodes. Shortly thereafter the child moved from the city of New York.

CASE 21.

Reaction to tuberculin	—	—	—	—	—10	±	+10	—	—	—	—	—	—0.2	—	—	—
Age in months	3	5	13	15	15	18	21	25	27	32	41	44	45	56	61	67

In this case a tuberculin test with 0.1 mg. when the patient was 18 months of age resulted in a mild reaction, with an induration 4 mm. in diameter. The response at 21 months of age to 10 mg. was 1 plus (10 mm. of redness and induration). Roentgenograms taken at these periods showed no evidence of tuberculosis.

It would appear reasonable to assume, therefore, that at least 3 of the 5 subjects in whom the reaction to tuberculin became positive (subjects 9, 11 and 19) were exposed to open tuberculosis at some time during the period of observation.

One may conclude, therefore, in view of the few cases in which sensitivity developed after frequent inoculations of tuberculin, that routine tuberculin tests will rarely if ever sensitize the skin to tuberculin.

It should also be pointed out that local sensitization does not develop, since all tests were performed on the left forearm and a negative reaction resulted in practically every instance.

TABLE 3.—*Reactions to High Doses of Old Tuberculin* *

| Subject | | |

TABLE 4.—*Results of Tuberculin Tests on Children Exposed to Persons with Tuberculosis* *

| Subject | | |

tuberculin on one occasion. As shown in table 3, the reactions were consistently negative.

Mention may be made of 13 additional children receiving frequent tuberculin tests, often with increased doses, who were not included among the 62 subjects in this study since they were exposed to tuberculous persons during some time while under observation. These children's reactions to tuberculin remained negative with only 2 exceptions (cases C and M, table 4), and in both of these sensitization developed only after exposure to bacillus-containing sputum.

The observations on these 27 subjects (tables 3 and 4), although the group is small, indicate that tuberculin, even when inoculated intradermally in greatly increased doses, does not cause sensitization of the tissues.

TABLE 5.—*Reactions of Patients Over Twelve Months of Age*

Subject Number	Number of Tests	Age Period in Months During Which Tests Were Performed
3	23	12 - 47
25	7	17 - 59
1	15	12 - 15
14	12	22 - 57
18	11	12 - 52
28	5	14 - 46
20	5	46 - 58
29	5	13 - 56
24	6	13 - 58
17	8	15 - 55
21	14	13 - 67
26	6	15 - 60
A	7	12 - 42
B	19	12 - 23
D	33	12 - 26
E	10	12 - 56
G	22	12 - 17
H	16	12 - 51
J	7	12 - 36

The suggestion presented in the preceding section of the paper that tuberculin tests at too frequent intervals might serve to build up a resistance to sensitization rather than to sensitize is not supported by our observations, since the testing of 42 children at intervals of two to twelve months has failed to show any development of sensitivity.

The further suggestions that many of the subjects here reported on received their frequent tests during the early months of life, at a time when the body is less capable of forming antibodies,[11] and that frequent testing of an older age group might produce greater frequency of sensitization are also unsupported, since a study of a number of cases, in all of which the patient received frequent tests after 12 months of age, failed to show any tendency to sensitization at this period, when a positive reaction to tuberculin is not infrequently seen (table 5).

11. Barnwell and Pollard.[7] Freund.[8]

It would seem, therefore, from the study of 62 subjects presented in this paper that there is little if any evidence that repeated intradermal inoculations of tuberculin, regardless of dosage or frequency of injections, cause development of sensitivity in the tissues.

SUMMARY AND CONCLUSIONS

Sixty-two children received frequent inoculations of tuberculin, ranging from 3 to 61, during periods of from one to five years. Doses of tuberculin varying from 0.1 mg. to 100 mg. were used for testing.

The results do not support the concept that cutaneous sensitization is induced by frequent inoculations with usual or even larger than usual doses of old tuberculin.

There was no evidence that local sensitization of the tissues results from repeated tuberculin tests in the same dermal area.

7 East Eighty-Second Street.

Case Reports

ARTERIOVENOUS ANGIOMA OF MANDIBLE AND RETINA WITH PRONOUNCED HEMATEMESIS AND EPISTAXIS

L. E. BOWER, M.D.

S. P. DITKOWSKY, M.D.

BERTHA A. KLIEN, M.D.

AND

I. P. BRONSTEIN, M.D.

CHICAGO

Epistaxis is a common symptom in childhood and frequently is accompanied by emesis of swallowed blood. When the underlying cause of these symptoms is an arteriovenous angioma of the mandible associated with a similar lesion of the retina, the case is of sufficient interest to merit report. Spurious epistaxis and hematemesis with the underlying lesion an angioma of the mandible have been reported by Broderick and Round [1] and Kroh.[2] These men reported instances in which fatal hemorrhage followed the extraction of a loose molar tooth.

The combination of a cavernous angioma of the mandible with an arteriovenous angioma of the retina has not been heretofore reported. Ocular conditions resembling that in this patient have been found by Krug and Samuels,[3] Feig [4] and Wernche.[5] In the patients of the two last-mentioned authors the malformation was discovered incidentally during a routine examination and did not affect the vision of these eyes. In the patient of Krug and Samuels the venous retinal angioma was associated with one of the optic nerves, chiasm and brain, and the patient

From the Children's Division of the Cook County Hospital and the Department of Pediatrics and Ophthalmology (Rush), University of Illinois College of Medicine.

1. Broderick, R. A., and Round, H.: Cavernous Angioma of Maxilla: Fatal Haemorrhage After Teeth Extraction, with Notes of Similar Non-Fatal Case, Lancet **2**:13, 1933.

2. Kroh, F.: Tooth Extraction and Spontaneous Fatal Hemorrhage, Arch. f. klin. Chir. **39**:389, 1925.

3. Krug, E., and Samuels, B.: Venous Angioma of the Retina, Optic Nerve, Chiasm and Brain: Case Report with Post-Mortem Observations, Arch. Ophth. **8**:871 (Dec.) 1932.

4. Feig, I.: A Case of Angioma Retinae, Brit. J. Ophth. **22**:295, 1938.

5. Wernche, T.: Angioma papillae nervi optici, Klin. Monatsbl. f. Augenh. **104**:435, 1941.

died of cerebral complications. In another of these patients [2] a retinal hemorrhage leading to partial loss of vision in the affected eye occurred late in life.

REPORT OF A CASE

A. L. (fig. 1), a white boy aged 9 years, entered the hospital for the first time on June 7, 1940. He had been referred from the otolaryngologic clinic, where he had been treated for severe epistaxis, with the impression that he probably had a blood dyscrasia.

Fig. 1.—Photograph of the patient at the time of his admission to the hospital.

History.—The delivery was full term and spontaneous, the weight at birth being 7½ pounds (3,402 Gm.). The neonatal period was normal, and his development was normal. He had had measles, mumps and influenza. At the age of 3 years he was seen by a physician because of a squint of the left eye. The mother was told that the eye would become corrected when the boy started to read. At the age of 6 years, the school physician examined the boy's eyes and informed the mother that he was blind in the left eye because of a defect in the vessels of the retina. No previous history of bleeding could be obtained.

There is no history of visual difficulties or neurologic problems in the family. A brother, aged 12, has a pigmented nevus in the left axilla.

The present illness began on May 30, 1940, when the patient vomited a large quantity of blood. This was repeated the following day and again three days later, at which time the emesis was accompanied by a severe nosebleed. On the day of admission the patient had a profuse epistaxis, which caused the mother to seek medical advice.

Physical Examination.—Examination on admission revealed a well developed and nourished boy who appeared acutely ill; the temperature was 102.8 F., the pulse rate 110, the respiratory rate 22 and the blood pressure 90 systolic and 50 diastolic. The skin and mucous membranes exhibited a pronounced pallor. The left side of his face appeared fuller and warmer than the right. There was an almost imperceptible bluish discoloration over the lower part of the left cheek. A thrill and bruit synchronous with the entire cardiac cycle were elicited over this area. The veins on the left side of the face were prominent. A small bluish discoloration was also present over the chin. The pupil of the left eye did not react to light, and objects could not be seen. Examination of the fundus of the left eye revealed

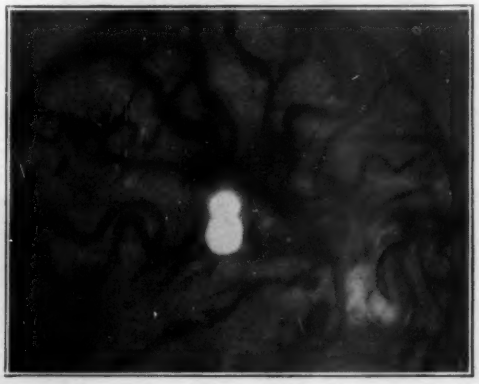

Fig. 2.—Photograph of the fundus of the left eye, showing the tremendously dilated and tortuous blood vessels.

a vascular anomaly, the description of which is given subsequently (fig. 2). The right eye was normal. The heart was enlarged to the left, and an apical systolic murmur was elicited. The liver was palpable 2 fingerbreadths below the costal margin.

Course.—The blood count on the child's admission revealed a hemoglobin content of 43 per cent, 7,450 white blood cells and 2,440,000 red cells. The differential count, bleeding and clotting time and platelet count were all normal.

Two days after his admission profuse bleeding from the nose occurred, followed by vomiting of large quantities of dark blood, which apparently had been aspirated. The patient complained of pain in the left lower jaw, focusing attention on the teeth. The first permanent left molar was loose in the socket, and movement of this tooth caused bleeding. Roentgenograms of the jaw revealed a large cystic area in the left mandible, which had been interpreted by the oral surgeons as an anomaly (fig. 3). Nine months later, a roentgenogram of the jaw failed to reveal any bony defects [fig. 4].) Seven days after entrance the patient twice had epistaxis and emesis of aspirated blood, the source of bleeding being from the area about the loose tooth. This tooth was extracted, and a pack was sutured in place.

Several transfusions had been given for the severe anemia which had developed. The blood count at this time showed 2,300,000 red cells and 7,000 white cells. The differential count showed 51 per cent polymorphonuclear leukocytes, 31 per cent

Fig. 3.—Roentgenogram of the jaw, showing the large cystic area in the left mandible.

Fig. 4.—Roentgenogram of the jaw, taken nine months later than figure 3, showing the absence of bony defects.

lymphocytes, 7 per cent monocytes and 1 per cent eosinophils. Two days after the insertion of the pack the jaw became severely swollen and the temperature rose to 105 F. The pack was removed by the surgeons, who believed that a secondary infection had occurred. The following day the patient complained of pain about

the submental regions, and the lower incisors were found to be loose and tender. Roentgenograms taken eight days after the onset of the infectious process suggested the presence of infection of the mandible about the incisor teeth as well as of several large cystic areas on the left side of the bone. The elevation of temperature persisted for ten days, being associated with chills. On the eleventh day a localized area of infection appeared over the chin. Aspiration of pus from this area resulted in an afebrile course. Repeated blood cultures during this period failed to show any organisms. Urinalysis occasionally showed a trace of albumin. As the patient began to improve, an attempt was made to discover the presence of associated visceral lesions. A search for a hemangioma of the nose was not successful. Roentgen studies of the gastrointestinal tract with barium sulfate and intravenous pyelograms showed nothing abnormal. Roentgenograms of the chest, skull, long bones and spine did not give indications of pathologic change. Visualization of the optic foramens did not reveal signs of erosion, but the left foramen appeared to be enlarged. Encephalography was attempted but was not successful, and consent for a reexamination was refused. Determinations of the calcium, cholesterol, cholesterol esters, nonprotein nitrogen, creatinine, phosphorus and phosphatase of the blood proved these to be of normal values. A dextrose tolerance test also yielded a normal result. The urinary diastase was within normal limits. Forty-five days after admission the boy was taken home, but he was readmitted on March 30, 1941 for consultation pertinent to treatment. At this time no progression of ocular symptoms was present. Roentgenograms of the jaw failed to reveal the cystic areas previously noted.

Ophthalmoscopic Examination.—Left fundus: From the optic disk, which was barely visible, emerged a large number of tremendously dilated and tortuous blood vessels, among which arterial and venous branches were barely distinguishable, all of them of a dark venous color. Some vascular branches in the neighborhood of the disk were dilated to three and four times the size of a normal retinal vessel and formed preretinal and prepapillary loops. One particularly broad vessel emerged from the superior nasal quadrant of the disk and then turned sharply backward, disappearing into the retina in the fashion of an opticociliary vein. These vessels reached their fields of distribution in the periphery of the fundus in a more or less tortuous course, straightening out considerably toward the periphery and losing much of their conspicuous dilatation, so that the periphery of the fundus, aside from the darker color of the vessels, appeared normal. There were no retinal nodes or tumors.

This fundus represented the visible retinal portion of a severe congenital vascular malformation which involved the left side of the face, as described in another part of this paper. The conglomeration of dilated tortuous and evenly dark-colored vessels, which replaced the retinal vascular tree, pointed to the existence of an arteriovenous communication.

The only condition of the fundus which might come into consideration for differential diagnosis in this case is the early stage of the angiomatosis retinae, or von Hippel's disease, in the pathogenesis of which the factor of maldevelopment has been emphasized of recent years. This condition is characterized by one or more reddish nodes in one or more sectors of the periphery of the fundus, situated in place of the capillary bed between a greatly altered vein and an artery. These vessels are enormously dilated and tortuous and show formation of aneurysms. At

least one artery enters into and one or two veins emerge from such a node. The optic disk and the remaining blood vessels are usually normal.

Since Cushing and Bailey's monograph of 1928,[6] wherein they considered the retinal tumors in von Hippel's disease as true hemangioblastomas, some evidence, based on the work of Knodel,[7] Roussy and Oberling [8] and Berger and Vallée,[9] has been brought forth to indicate that the conception of these tumors as angiomatous malformations rather than true blastomas is justified. Van der Hoeve,[10] who developed the conception of the so-called phakomatoses, and others called attention to a group of congenital disorders in which defects of the central nervous system are associated with visceral and cutaneous malformations, e. g. Bournville's tuberous sclerosis, von Recklinghausen's neurofibromatosis, encephalotrigeminal angiomatosis and Sturge-Weber disease.

In contradistinction to the systemic and capillary type of angiomatoses in the Hippel-Lindau and Sturge-Weber syndromes, the patient discussed here had a localized, if extensive, angiomatous malformation of the arteriovenous type, as indicated by its visible retinal portion and the presence of a bruit and thrill over the lesion. The enlarged left bony optical canal, as seen in the roentgenograms, suggests the possibility that the optic nerve in its entire course contains angiomatous vessels, as was the case in the patient of Krug and Samuels.[3]

From the clinical aspect it cannot be decided whether this angioma is of the congenital arteriovenous type, representing a retention of the original arteriovenous connections, or whether it was originally a venous angioma and has undergone a process of arterialization.

COMMENT

Ward and Horton [11] have suggested that the term abnormal arterial venous communication be applied to all vascular anomalies in which blood passes into the venous system without passing through the capillary bed. Thus arteriovenous aneurysms, arteriovenous fistulas and angiomas

6. Cushing, H., and Bailey, P.: Hemangiomas of Cerebellum and Retina, Arch. Ophth. **57**:447, 1928.

7. Knodel, G.: Zur Kenntnis der v. Hippelschen Erkrankung (Angiomatosis Retinae), Virchows Arch. f. path. Anat. **281**:886, 1931.

8. Roussy, G., and Oberling, C.: Les tumeurs angiomateuses des centres nerveux, Presse méd. **38**:179, 1930.

9. Berger, L., and Vallée, A.: L'angio-reticulo-xanthome de la rétine. Contribution à l'étude des maladies de von Hippel et de Lindau, Ann. d'anat. path. **8**:313, 1931.

10. van der Hoeve, J., in transactions of the Oxford Ophthalmological Congress, 1933; abstracted, Zentralbl. f. d. ges. Ophth. **29**:394, 1933.

11. Ward, C. E., and Horton, B. T.: Congenital Arteriovenous Fistula in Children, J. Pediat. **16**:746, 1940.

represent the same type of lesion, which may be demonstrated by arteriography or by an increase in oxygen content of the venous blood adjacent to such a region. In their studies of 44 patients with vascular anomalies of the arteriovenous type occurring in children, 4 had involvement of the scalp, face and neck. Abnormal ocular conditions were not noted in these children.

The normal roentgenograms of the mandible obtained during the second admission to the hospital can be explained on the basis of the fibrotic changes which occurred secondary to the infectious process.

Cardiac hypertrophy and systolic murmurs are often found associated with abnormal arteriovenous communications. The association of the cardiac abnormalities with the symptoms of epistaxis suggested the possibility of rheumatic heart disease. As pointed out in the first paragraph of this paper, a possible cause for such bleeding may be the rare phenomenon which our patient exhibited. Inasmuch as this is a rare condition, it may give rise to a diagnostic error. This also emphasizes the necessity for examining the teeth and jaw in the search for an obscure cause for hematemesis or epistaxis.

SUMMARY AND CONCLUSIONS

A case is reported of an arteriovenous angioma of the mandible and retina.

An obscure cause for spurious hematemesis and epistaxis may be a vascular lesion of the jaw with bleeding around the teeth.

5919 Forest Glen Avenue.
Cook County Hospital.
7427 South Shore Drive.
1819 West Polk Street.

PAROXYSMAL VENTRICULAR TACHYCARDIA IN CHILDHOOD

FRANCIS F. ROSENBAUM, M.D.

FRANKLIN D. JOHNSTON, M.D.

AND

ARTHUR P. KELLER, M.D.

ANN ARBOR, MICH.

Paroxysmal ventricular tachycardia is an ectopic cardiac rhythm consisting of a rapid succession of ventricular extrasystoles. Although graphic records in paroxysmal rapid heart action had been made some time earlier [1] and Mackenzie [2] had pointed out that the underlying mechanism in such disturbances is not always the same, Lewis [3] first differentiated supraventricular tachycardia from tachycardia of ventricular origin by means of electrocardiograms. He was able to produce ventricular tachycardia in experimental animals by coronary ligation.[4] This arrhythmia has subsequently been induced experimentally by a variety of procedures.[5]

Numerous cases of ventricular tachycardia have been reported in the literature, but many do not meet the criteria which seem necessary

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From the Department of Internal Medicine and the Department of Pediatrics and Communicable Diseases, University of Michigan Medical School.

1. Cotton, R. P.: Notes and Observations upon a Case of Unusually Rapid Action of the Heart (232 per Minute), Brit. M. J. **1**:629 (June 1) 1867.

2. Mackenzie, J.: Diseases of the Heart, London, Oxford University Press, 1908, p. 166.

3. Lewis, T.: Single and Successive Extra-Systoles, Lancet **1**:382 (Feb. 6) 1909.

4. Lewis, T.: Paroxysmal Tachycardia, Heart **1**:43 (July) 1909; The Experimental Production of Paroxysmal Tachycardia and the Effects of Ligation of the Coronary Arteries, ibid. **1**:98 (Nov.) 1909.

5. (*a*) Levy, A. G., and Lewis, T.: Heart Irregularities, Resulting from the Inhalation of Low Percentages of Chloroform Vapour, and Their Relationship to Ventricular Fibrillation, Heart **3**:99 (Oct.) 1911. (*b*) Rothberger, C. J., and Winterberg, H.: Ueber die experimentelle Erzeugung extrasystolischer ventrikulärer Tachykardie durch Acceleransreizung, Arch. f. d. ges. Physiol. **142**: 461 (Oct. 30) 1911. (*c*) Felberbaum, D.: Paroxysmal Ventricular Tachycardia: Report of a Case of Unusual Type, Am. J. M. Sc. **166**:211 (Aug.) 1923. (*d*) Piccione, F. V., and Scherf, D.: The Rhythmic Formation of Coupled Beats and Paroxysmal Tachycardias in the Outer Layers of the Myocardium, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **3**:83 (June) 1940.

for this diagnosis. In 1930, Strauss [6] found 65 acceptable cases, while in 1934 Lundy and McLellan [7] considered that only 96 out of a total of 152 cases fulfilled the diagnostic requirements. Robinson and Herrmann [8] pointed out that to permit the diagnosis there must be indications that the tachycardia is due to impulses arising in the ventricles, that is, the QRS complexes in the electrocardiogram must have the ventricular form. They further indicated that electrocardiographic evidence of a slower, independent auricular rhythm is one of the clearest proofs of the ventricular origin of the tachycardia. However, since their report cases have been recorded in which ventricular tachycardia has been associated with auricular fibrillation.[9] auricular flutter [10] or retrograde activation of the auricles with 1 : 1 response [11] or partial block.[12] Occasionally in ventricular tachycardia the electrocardiograms will show P waves although no definite auricular rhythm can be made out, and in still other cases there are no definite P waves at all.[13]

The diagnosis of paroxysmal ventricular tachycardia can be made with certainty only when the nature of the auricular activity is clear; otherwise it may be confused with supraventricular tachycardia with aberrant ventricular responses [14] or supraventricular tachycardia occur-

6. Strauss, M. B.: Paroxysmal Ventricular Tachycardia, Am. J. M. Sc. **179**:337 (March) 1930.

7. Lundy, C. J., and McLellan, L. L.: Paroxysmal Ventricular Tachycardia: An Etiological Study with Special Reference to Type, Ann. Int. Med. **7**:812 (Jan.) 1934.

8. Robinson, G. C., and Herrmann, G. R.: Paroxysmal Tachycardia of Ventricular Origin, and Its Relation to Coronary Occlusion, Heart **8**:59 (Feb.) 1921.

9. Gallavardin, L.: Tachycardie ventriculaire terminale: Succédant à une arythmie complète et compliquée de troubles rhythmiques divers (tachycardie supra-ventriculaire et troubles de la conductibilité), Arch. d. mal. du cœur **13**:207 (May) 1920. Bunn, W. H.: Ventricular Tachycardia, Rate of 300, Following Thyroidectomy, Am. Heart J. **8**:714 (June) 1933.

10. Gallavardin, L.: Tachycardie ventriculaire terminale: Greffeé sur une tachysystolie auriculaire, Arch. d. mal. du cœur **13**:210 (May) 1920.

11. Scott, R. W.: Observations on a Case of Ventricular Tachycardia with Retrograde Conduction, Heart **9**:297 (Dec.) 1922. Wilson, F. N.; Wishart, S. W.; Macleod, A. G., and Barker, P. S.: A Clinical Type of Paroxysmal Tachycardia of Ventricular Origin in Which Paroxysms Are Induced by Exertion, Am. Heart J. **8**:155 (Dec.) 1932.

12. Hart, T. S.: Paroxysmal Tachycardia: The Paroxysms Arise from Impulses of Ventricular Origin; the Auricle Responds to the Ventricle; Evidence of Two Points of Abnormal Ventricular Irritability, Heart **4**:128 (Nov.) 1912.

13. Prinzmetal, M., and Kellogg, F.: On the Significance of the Jugular Pulse in the Clinical Diagnosis of Ventricular Tachycardia, Am. Heart J. **9**:370 (Feb.) 1934.

14. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, Shaw & Sons, Ltd., 1925, p. 255. White, P. D., and Stevens, H. W.: Ventricular Response to Auricular Premature Beats and to Auricular Flutter, Arch. Int. Med. **18**:712 (Nov.) 1916.

ring in a person who has a defect in intraventricular conduction even with a normal rate.[15] Some of the examples of ventricular tachycardia reported in the literature are undoubtedly instances of one or the other of these two conditions. If the signs of auricular activity during the paroxysm of rapid heart action are not clear, other electrocardiographic evidence may be present which favors the diagnosis of tachycardia of ventricular origin. This may consist of isolated ventricular extrasystoles of the same form as the QRS complexes during the tachycardia, or a record of the onset of the attacks, or a record of the offset without a postparoxysmal pause or tachycardia of ventricular form occurring in the presence of known, long-standing auricular fibrillation.

There are clinical observations which are often helpful in distinguishing ventricular tachycardia from other forms of paroxysmal rapid heart action. At times variations in the length of successive heart cycles can be detected.[16] Frequently, owing to changing relations between auricular and ventricular systole, there are variations in the quality and intensity of the first heart sound at the apex.[17] This sign will be present in those subjects whose auricles are beating normally and independently. Prinzmetal and Kellogg [13] found in this type of patient a prominent jugular pulse which was slower than the apical heart rate. Finally, vagal stimulation by either carotid or ocular pressure may serve to differentiate supraventricular tachycardia from that arising in the ventricle, since it frequently causes the former to cease abruptly whereas it has no effect on the latter.

Until recent years the number of cases of paroxysmal rapid heart action in children reported in the literature was small. In 1932, Shookoff, Litvak and Matusoff [18] were able to find only 40 cases. In 1937, Taran and Jennings,[19] using the age of 15 as their upper limit, were able to add 12 cases. A more recent report by Johnson [20] brought the total to 63. Only 4 of these cases had been reported by the original observers as examples of ventricular tachycardia. Hubbard [21] reported 9 cases of

15. Marvin, H. M., and White, P. D.: Observations on Paroxysms of Tachycardia, Arch. Int. Med. **29**:403 (April) 1922.

16. Strong, G. F., and Levine, S. A.: The Irregularity of the Ventricular Rate in Paroxysmal Ventricular Tachycardia, Heart **10**:125 (April) 1923.

17. Levine, S. A.: The Clinical Recognition of Paroxysmal Ventricular Tachycardia, Am. Heart J. **3**:177 (Dec.) 1927.

18. Shookoff, C.; Litvak, A. M., and Matusoff, I.: Paroxysmal Tachycardia in Children: Report of Four Cases and One Postmortem Examination, Am. J. Dis. Child. **43**:93 (Jan.) 1932.

19. Taran, L. M., and Jennings, K. G.: Paroxysmal Atrioventricular Nodal Tachycardia in a New-Born Infant, Am. J. Dis. Child. **54**:557 (Sept.) 1937.

20. Johnson, G. D.: Paroxysmal Tachycardia in Children, Am. J. Dis. Child. **60**:1137 (Nov.) 1940.

21. Hubbard, J. P.: Paroxysmal Tachycardia and Its Treatment in Young Infants, Am. J. Dis. Child. **61**:687 (April) 1941.

supraventricular tachycardia in infants and collected 19 more from the literature, all the patients being less than 1 year of age. Because 6 of his cases were observed within a year, it was his belief that this disorder is more common than is generally believed.

A review of the literature has disclosed 7 cases of paroxysmal ventricular tachycardia in patients 15 years of age or younger.[22] All but 1 of these have been reported within the last six years. The more significant data regarding them have been summarized in the accompanying table. There were 5 boys and 2 girls. The youngest patient was 15 months old. There was no common underlying cardiac disease, and in the majority there was little evidence of organic heart disease. Two of the children died; in 2 others the rhythm reverted to normal after the administration of quinidine, and the others apparently recovered spontaneously. In 5 the attacks occurred repeatedly over periods of from three to five years.

Six additional cases [23] have been reported as examples of paroxysmal ventricular tachycardia in childhood, but, although they may be instances of this disorder, the data presented do not fulfil the diagnostic criteria. In none of them can evidence of auricular activity be made out in the

22. (*a*) Amberg, S., and Willius, F. A.: Clinic on Ventricular Tachycardia Occurring in an Infant: Cardiac Hypertrophy of Unknown Origin; Course; Postmortem Findings; Comment; Discussion, Proc. Staff Meet., Mayo Clin. **13**:470 (July 27) 1938. (*b*) Campbell, M.: Paroxysmal Tachycardia in Infants, Guy's Hosp. Rep. **87**:205 (April) 1937. (*c*) Stern, N. S.: Paroxysmal Ventricular Tachycardia: Report of Three Cases; Mecholyl Used and Ineffective in Two, Ann. Int. Med. **11**:519 (Sept.) 1937. (*d*) Levine, S. A., and Beeson, P.: The Wolff-Parkinson-White Syndrome with Paroxysms of Ventricular Tachycardia, Am. Heart J. **22**:401 (Sept.) 1941. (*e*) Harvey, A. M.: The Origin of Paroxysmal Tachycardias as Determined by the Esophageal Electrocardiogram, Ann. Int. Med. **11**:57 (July) 1937. (*f*) Schliephake, E.: Der kardio-intestinale Symptomenkomplex bei der progressiven Muskeldystrophie; graphische Untersuchungen, Ztschr. f. Kinderh. **47**:85 (Jan.) 1929. (*g*) von Bernuth, F.: Ueber paroxysmale Tachykardie im Kindesalter, ibid. **47**:94 (Jan.) 1929.

23. Rubell, I., and Strauss, H.: Fatal Paroxysmal Tachycardia in a Young Child, Am. J. Dis. Child. **51**:633 (March) 1936. Hamburger, W. W.: Bundle Branch Block: Four Cases of Intraventricular Block Showing Some Interesting and Unusual Clinical Features, M. Clin. North America **13**:343 (Sept.) 1929. Laurentius, P.: Beitrag zur aktiven heterotopen Reizbildungsstörung des Herzens im Kindesalter (paroxysmale Tachykardie), Monatschr. f. Kinderh. **77**:30 (Jan. 14) 1939. Franke, W., and Weiner, R.: Die paroxysmale Tachykardie im Kindesalter, Ztschr. f. Kinderh. **46**:676 (Dec.) 1928. Moore, H.: Paroxysmal Ventricular Tachycardia, Irish J. M. Sc., 1928, p. 754. Navarro, J. C., and Huergo, C. A.: Taquicardia paroxística de origen ventricular en una niña de doce años, Prensa méd. argent. **20**:1179 (May 31) 1933.

Summary of Recorded Cases of Ventricular Tachycardia in Patients 15 Years Old or Younger

No.	Sex	Age	History	Physical Examination	Treatment	Outcome	Cardiac Diagnosis
1. Amberg and Willius [22a]	F	15 mo.	Diarrhea followed by cough, dyspnea and anorexia which persisted; later loss of weight and difficulty in feeding	Heart enlarged; no murmurs; ventricular rate 200/min.; auricular rate 75/min.; rales throughout chest; roentgenogram showed moderate cardiac enlargement and pulmonary congestion	Supportive	Died; autopsy showed left ventricular hypertrophy and dilatation of all chambers	Idiopathic cardiac hypertrophy
2. Campbell [22b]	M	20 mo.	Irritability, abdominal pain, collapse and anorexia; recurrent for 3 weeks	Heart not abnormal; ventricular rate 274/min.; auricular rate 128/min.; liver much enlarged	Tinct. of digitalis, 2 minims (0.12 cc.) 4 times a day	Spontaneous recovery; patient well 5 yr. later	None
3. Stern [22c]	M	7 yr.	Repeated bouts of tachycardia associated with nausea, vomiting and precordial pain; attacks over 5 yr. period; lasting a few hours to 2½ days	Heart not abnormal; ventricular rate about 200/min.	Mecholyl, without effect; quinidine in small doses, occasionally of prophylactic benefit	Spontaneous recovery from attacks; patient well 5 yr. after first attack	"Definite myocardial disease"
4. Stern [22c]	M	8 yr.	Abdominal pain and tachycardia	Heart enlarged, soft systolic murmur; enlargement confirmed by roentgenogram; liver slightly enlarged; ventricular rate about 200/min.	Mecholyl, without effect; quinidine up to 19 grains (1.23 Gm.) in 10 hours ineffective	First attack stopped sponaneously after 8 days; second attack 3 mo. later and death on third day; no autopsy	Cardiac enlargement, cause unknown
5. Levine and Beeson [22d]	M	13 yr.	Sudden onset, with weakness, dyspnea, retrosternal pain and vomiting	Heart not enlarged; loud first sound at apex; no murmurs; heart rate 292/min.; roentgenogram normal	Morphine; digalen, 2.0 cc.; quinidine, 0.2 Gm.; in 40 min., cessation of tachycardia	Recovery after quinidine; patient well 1 yr. later	Wolff-Parkinson-White syndrone
6. Harvey [22e]	F	15 yr.	Sense of choking, vomiting and tachycardia; two previous attacks, the first at age of 13	Heart at upper limits of normal in size; no signs of heart failure; ventricular rate 230/min.	Apomorphine, with temporary effect; mecholyl ineffective; after total of 1 Gm. of quinidine, cessation of tachycardia	Recovery after quinidine	(?) rheumatic heart disease
7. Schliephake [22f] von Bernuth [22g]	M	15 yr.	Repeated bouts of tachycardia associated with fever over period of several months	Advanced pseudohypertrophic muscular dystrophy; no cardiac abnormalities; ventricular rate 160/min.	Supportive	Spontaneous recovery from attacks	None

electrocardiograms which have been published, nor is there adequate supportive evidence for the diagnosis. Furthermore, 4 cases [24] have been recorded in which the paroxysms of tachycardia began during childhood but the patients were over the age of 15 when electrocardiographic observations were made regarding the type of rapid heart action.

Two examples of paroxysmal ventricular tachycardia in children have recently been observed in this clinic. These cases exhibited unusual and interesting features.

REPORT OF CASES

CASE 1.—*Congenital heart disease; paroxysmal ventricular tachyacrdia of two weeks' duration; reversion to normal rhythm after large doses of quinidine.*

J. B., an 8½ year old boy, was admitted to the University Hospital on June 6, 1941, complaining of shortness of breath and rapid heart beat. His had been an instrumental delivery, but he was normal at birth, and cyanosis had not been noted. At the age of 1 week it was observed that his heart was beating rapidly, and a physician reported that the heart was "enlarged and leaking." At the age of 6 months a consultant noted a loud systolic murmur over the precordium, most intense over the sternum. A roentgenogram of the chest at that time was said to have shown evidence of tuberculosis in the upper lobes of each lung but a statement was not made regarding the heart. His development had been normal, and he had always been normally active. The only abnormalities which his parents had observed in him were an anterior bulging of the sternum and a constant, forceful, somewhat rapid heart beat. He had had pneumonia, chickenpox, measles and two attacks of otitis media. A tonsillectomy, performed with the patient under general anesthesia, at the age of 4 years was uneventful. The family history was not significant.

On the afternoon of May 22, 1941, he complained of cramping pain in the upper part of the abdomen. This abated spontaneously but recurred during the night, at which time it was relieved by food. The next morning he complained of general malaise and went to school only after some urging. During the noon recess, while playing tag, he felt his heart suddenly begin to beat rapidly. Within a few minutes severe abdominal pain made its appearance. The child became frightened and went home. Shortly thereafter nausea and vomiting developed. A physician confirmed the presence of tachycardia and confined the patient to bed. All the symptoms persisted; he grew restless and complained of thirst but was unable to retain fluids.

On the morning of May 24, pallor and dyspnea were noted. The child was hospitalized, placed in an oxygen tent and given digitalis. The nausea and vomiting cleared, but the tachycardia, dyspnea and abdominal pain persisted. When the nausea and vomiting recurred after a few days, the digitalis was discontinued. During the second week of his illness he received a total of approximately 9.4 Gm. (140 grains) of quinidine without apparent benefit. Because of failure to respond to treatment, he was transferred to the University Hospital.

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24. Jones, T. D., and White, P. D.: Paroxysmal Ventricular Tachycardia: Report of an Unusual Case, Am. Heart J. **2**:139 (Dec.) 1926. Wolferth, C. C., and McMillan, T. M.: Paroxysmal Ventricular Tachycardia: Report of One Case with Normal Type of Auricular Mechanism and Three with Auricular Fibrillation, Arch. Int. Med. **31**:184 (Feb.) 1923. Major, R. H., and Wahl, H. R.: Paroxysmal Tachycardia Associated with Focal Myocarditis, J. A. M. A. **86**: 1125 (April 10) 1926. Willius, F. A.: Paroxysmal Tachycardia of Ventricular Origin, Boston M. & S. J. **178**:40 (Jan. 10) 1918.

Physical Examination.—The patient was a normally developed, well nourished boy, who appeared acutely ill. The facies was pinched and anxious. There was moderate orthopnea as well as slight cyanosis of the nailbeds, lips and ears. His temperature was 101.6 F. by rectum, his pulse rate 190 per minute and his respiratory rate 40 per minute. Examination of the thorax revealed a pronounced forward bulging of the sternum. There were a marked systolic precordial heave and a systolic thrill palpable along the left sternal margin. The heart was greatly enlarged. The heart rate was 190 per minute, with regular rhythm unaffected by ocular pressure or stimulation of the carotid sinus. There was a loud systolic murmur audible over the entire precordium, most intense in the region of the left nipple. There was also a questionable low-pitched protodiastolic sound at the apex. Although not noted on the initial examination, a few hours later definite variations in the intensity of the first heart sound at the apex were detected. The blood pressure

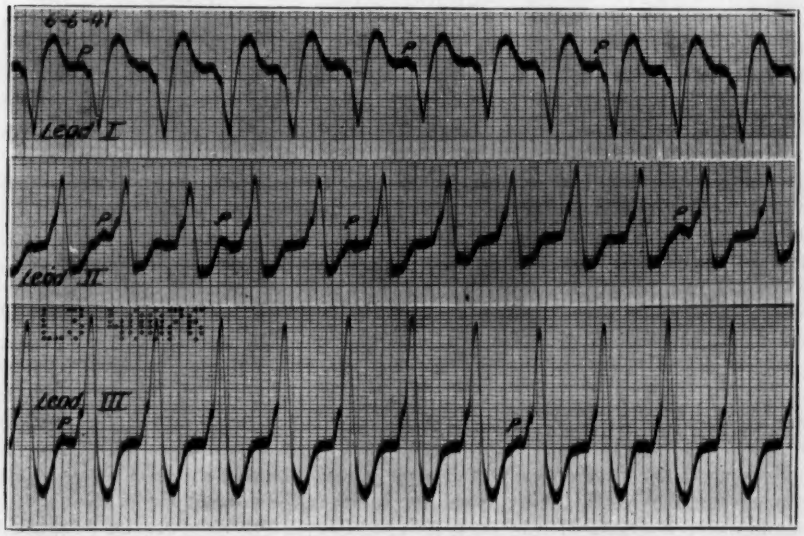

Fig. 1 (case 1).—Electrocardiogram taken on the patient's admission, June 6, 1941. Paroxysmal ventricular tachycardia is present, with a ventricular rate of 192.6 per minute, and an independent auricular rhythm, with a rate of 107 per minute. P waves are indicated in all leads.

was 94 systolic and 70 diastolic. The pulmonary fields were clear except for occasional rales at the base of the left lung posteriorly. The liver extended 1 handbreadth below the right costal margin in the midclavicular line and was exquisitely tender. Minimal pitting edema of the ankles was present. There was no clubbing of the fingers or toes. The physical examination was not otherwise abnormal.

Laboratory Data.—On admission the urine showed albumin (1 plus), 5 to 10 leukocytes per high power field and many hyaline and fine granular casts. One week later the urine was normal. The examination of the blood disclosed a hemoglobin content of 77 per cent (Sahli), 3,450,000 red cells and 9,900 white cells per cubic millimeter, with a normal differential count. On June 7, the nonprotein nitrogen content of the blood was 49 mg. per hundred cubic centimeters, and the chloride

content was 390 mg. per hundred cubic centimeters. Four days later these same determinations were 39 and 423 mg. respectively.

Electrocardiograms and Clinical Course.—The electrocardiogram taken on admission to the hospital (fig. 1 and fig. 2 *A*) revealed a tachycardia of ventricular origin, with a ventricular rate of 192.6 per minute. Definite P waves could be seen in all leads, indicating an independent auricular rhythm with a rate of 107 per minute. Thereupon, the patient was given quinidine sulfate. On the first day in the hospital he received six doses of 0.2 Gm. (3 grains) each at hourly intervals. This was ineffective, but the patient exhibited no intolerance for the medication. On the morning of the second day in the hospital he was given 0.4 Gm. (6 grains) hourly for five doses; then he received 0.6 Gm. (9 grains) hourly for 2 doses, and

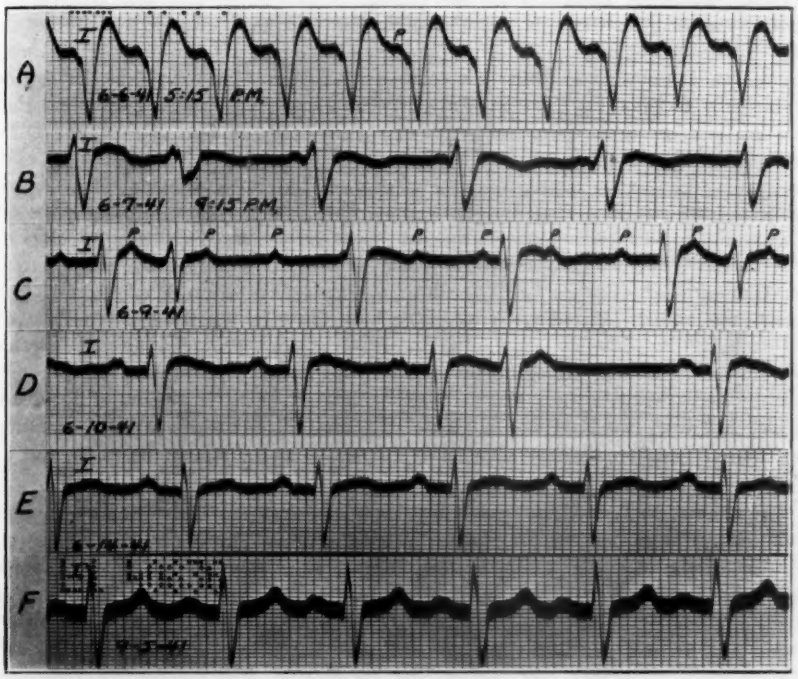

Fig. 2 (case 1).—*A*, lead I of the electrocardiogram made on admission June 6, 1941. *B*, lead I, June 7, 1941, after 4.8 Gm. (72 grains) of quinidine had been given in twenty-two hours. Independent auricular and ventricular rhythms are present. The second beat is a bizarre ventricular response to a premature auricular impulse. *C*, lead I, June 9, 1941. Independent auricular and ventricular rhythms are still present, but there is now auricular tachycardia, with a rate of 182 per minute. Occasional ventricular responses to supraventricular impulses are present. *D*, lead I, June 10, 1941. Normal sinus rhythm with occasional premature ventricular beats. *E*, lead I, June 14, 1941, after quinidine had been omitted for forty-eight hours. *F*, lead I, Sept. 5, 1941, at the time of reexamination.

finally he had an additional dose of 0.4 Gm. (6 grains). Thus, a total of 4.8 Gm. (72 grains) was administered within twenty-two hours. With this regimen the heart rate continued at the admission level until the late afternoon of the patient's

second day in the hospital, when it fell gradually to about 100 per minute and the rhythm became irregular.

An electrocardiogram taken twenty-six hours after the quinidine therapy was begun (fig. 2 *B*) disclosed a slow idioventricular rhythm, with a rate of 86 per minute. Definite P waves were again seen, and the independent auricular rate was nearly identical with that of the ventricles, which suggested that the two centers might be linked in some fashion. However, the auricular center apparently escaped from this linkage from time to time, giving rise to premature auricular impulses with bizarre ventricular responses which disturbed the idioventricular rhythm (second beat in figure 2 *B*). This was therefore dissociation with interference. The quinidine was discontinued for thirty-six hours after this record was made.

On June 9 the electrocardiogram (fig. 2 *C*) showed an auricular tachycardia, with a rate of 182 per minute, and an independent ventricular rhythm made irregular by occasional responses to the supraventricular impulses as well as ventricular extrasystoles, which had the same outline as the ventricular complexes during the ventricular tachycardia. These records on June 7 and June 9 showed an interesting feature in addition to the disturbances of rhythm. In the first of them the QRS complexes representing the idioventricular rhythm were fourteen hundredths of a second in duration, whereas those inscribed two days later, although of the same general form and thus from the same focus, were only ten hundredths of a second in duration. Furthermore, the occasional responses to supraventricular impulses in the former (fig. 2 *B*) were bizarre, whereas two days later they were normal in configuration (fig. 2 *C*). The abnormalities in the form of the ventricular complexes and the arrhythmias may have been the result of the prolonged period of tachycardia, although these alterations were more profound and of greater duration than those observed under similar circumstances by Graybiel and White [25] and by Gallavardin.[26] It seems more probable that the large amount of quinidine which had been necessary was chiefly responsible, since changes of this order due to large doses of quinidine have been observed both in human beings [27] and in experimental animals.[28]

Beginning on June 9, the patient was placed on a maintenance dose of quinidine, 0.2 Gm. (3 grains) every four hours during the day. The electrocardiograms on the following day (fig. 2 *D*) revealed normal sinus rhythm for the first time. Frequent auricular and ventricular premature beats were present, and the PR

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25. Graybiel, A., and White, P. D.: Inversion of the T-wave in Lead I or II of the Electrocardiogram in Young Individuals with Neurocirculatory Asthenia, with Thyrotoxicosis, in Relation to Certain Infections, and Following Paroxysmal Ventricular Tachycardia, Am. Heart J. **10**:345 (Feb.) 1935.

26. Gallavardin, L.: Tachycardie paroxystique ventriculaire avec conservation du rhythme auriculaire normal: Caractères du pouls veineux; enrégistrement de la terminaison de l'accès, Arch. d. mal. du cœur **13**:121 (March) 1920.

27. (*a*) Lewis, T.; Drury, A. N.; Wedd, A. M., and Iliescu, C. C.: Observations upon the Action of Certain Drugs upon Fibrillation of the Auricles, Heart **9**:207 (April) 1922. (*b*) Strong, G. F., and Munroe, D. S.: Paroxysmal Ventricular Tachycardia, with Report of an Unusual Case, Am. Heart J. **19**:486 (April) 1940.

28. Drury, A. N.; Horsfall, W. N., and Munly, W. C.: Observations Relating to the Action of Quinidine upon the Dog's Heart: The Refractory Period of, and Conduction in, Ventricular Muscle, Heart **9**:365 (Dec.) 1922.

and QRS intervals were at the upper limits of normal. Reexamination of the heart at this time revealed essentially the same conditions as on admission except that the systolic murmur was now loudest in the third intercostal space at the left sternal margin. The pulmonic second sound was easily heard but was not accentuated. At the apex the first heart sound was fairly loud, and at times a low-pitched diastolic murmur without presystolic accentuation could be heard.

The patient showed striking progressive symptomatic improvement beginning from the time of cessation of the tachycardia. The dyspnea, edema and cyanosis cleared rapidly. The liver decreased in size and grew less tender. The child became able to take food and fluids and gained strength. He was allowed to sit up in a chair on the twelfth day in the hospital and was discharged home on the following day.

He returned on September 5 for reexamination. His convalescence had been uneventful, and he had been free from symptoms except for occasional aching distress in the epigastrium. The usual pulse rate at rest had been 80 per minute,

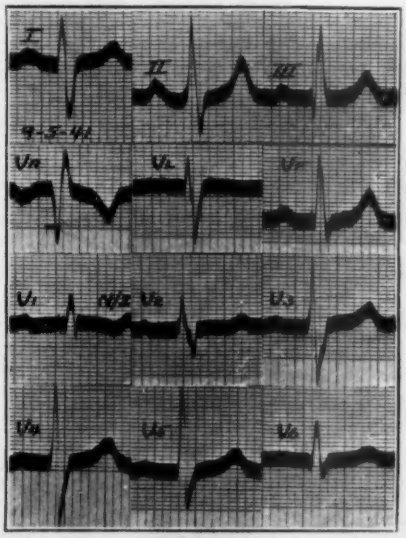

Fig. 3 (case 1).—Standard leads, extremity potentials and precordial leads on Sept. 5, 1941. V_1 shows a late second upstroke (R′), and lead I, V_5 and V_6 show deep, broad S waves. The curves are suggestive of incomplete right bundle branch block and right ventricular hypertrophy.

rising to 120 per minute after mild exertion. Extrasystoles, frequent at discharge, had gradually cleared. Quinidine had been gradually reduced to 0.2 Gm. (3 grains) every other day. The conditions observed on examination of the heart were the same as at the time of discharge. A tender edge of the liver was palpable 5 cm. below the costal margin in the right midclavicular line. The examination was not otherwise remarkable. The electrocardiograms at this time (fig. 2 *F* and fig. 3) showed broad QRS complexes with deep broad S waves in lead I, as did all the records taken during normal sinus rhythm. This had been thought to be due to the quinidine he was receiving (fig. 2 *D*), but persistence after the drug had been omitted for forty-eight hours (fig. 2 *E*) indicated that that was not the cause. One of the many sets of multiple precordial leads which were taken is shown in figure 3. The leads from the right precordium (V_1) show a late second upward deflection (R′), whereas those from the left precordium (V_5 and V_6) exhibit deep,

broad S waves. According to the studies of Wilson and his co-workers,[29] such tracings are indicative of either incomplete right bundle branch block or right ventricular hypertrophy. Examples of both right and left bundle branch block in association with Roger's disease have been recorded in the literature,[30] and it may be that in this case the interventricular septal defect was so located as to involve the right branch of the bundle of His. However, there was both clinical and roentgenologic evidence of cardiac enlargement in this patient, and this too may have played a role in the electrocardiographic abnormalities.

Roentgen Examination.—Roentgen studies of the thorax (fig. 4) made 5 days after cessation of the tachycardia revealed pronounced cardiac enlargement involving all chambers and moderate pulmonary congestion. The lateral view showed encroachment on the retrocardiac space except at its most inferior portion and

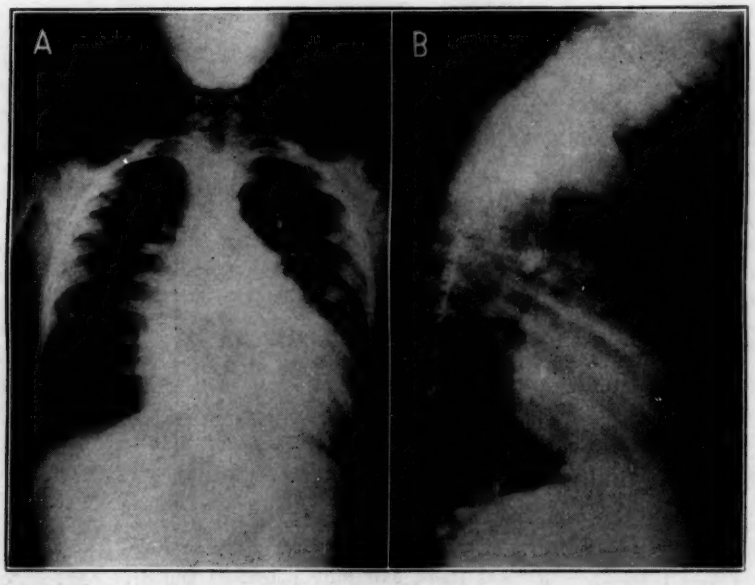

Fig. 4 (case 1).—Roentgenogram of chest, June 12, 1941. Note gross cardiac enlargement, encroachment on retrocardiac space and anterior bulging of the sternum.

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29. Wilson, F. N.; Johnston, F. D.; Hill, I. G. W.; Macleod, A. G., and Barker, P. S.: The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S-Deflections in Lead I, Am. Heart J. **9**:459 (April) 1934. Wilson, F. N.: Recent Progress in Electrocardiography and Interpretation of Borderline Electrocardiograms, Proc. A. Life Insur. M. Dir. America **24**:96 (Oct.) 1937.

30. Van der Kloot, A.: Congenital Bundle Branch Block as a Result, Probably, of a Defect in the Interventricular Septum: Report of a Case, Am. Heart J. **19**:623 (May) 1940. Schnitker, M. A.: The Electrocardiogram in Congenital Cardiac Disease, Cambridge, Mass., Harvard University Press, 1940, p. 68. Abbott, M. E., and Weiss, E., in Blumer, G.: Bedside Diagnosis, Philadelphia, W. B. Saunders Company, 1928, vol. 2, p. 427.

confirmed the presence of precordial bulging, a condition which Abbott [31] recorded in 5 of 50 cases in which an interventricular septal defect was considered the primary congenital cardiac anomaly. Roesler [32] has observed that in Roger's disease the heart is either normal in size on roentgen examination or there is moderate cardiac enlargement of the globular type. He stated further that if there is great prominence of the conus arteriosus, of the pulmonic arch or of the intrapulmonic vessels together with considerable right-sided enlargement other associated congenital cardiac anomalies must be considered. This boy exhibited gross cardiac enlargement, and although the exact nature of the accompanying defects is unclear, it seems certain that the interventricular septal defect was not the sole abnormality present.

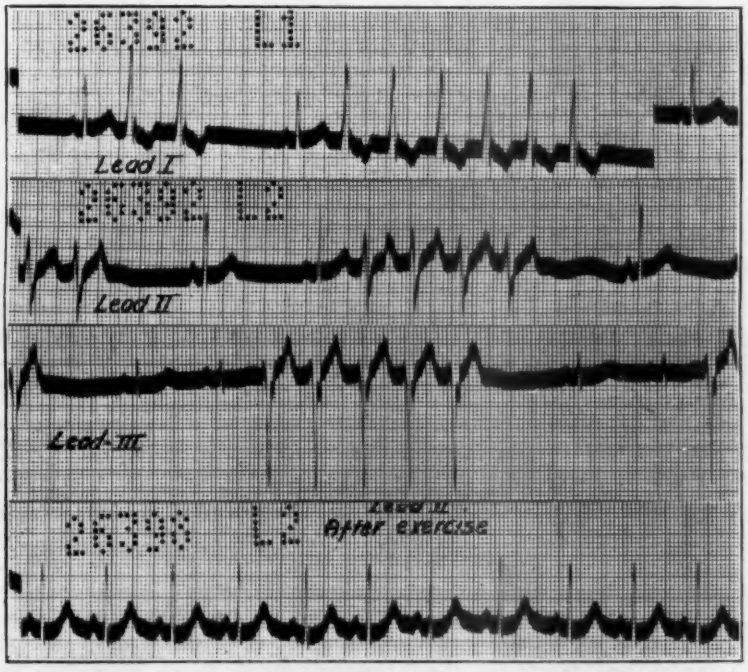

Fig. 5 (case 2).—The upper three records are standard leads on the patient's admission, on Jan. 4, 1937. All leads show short paroxysms of ventricular tachycardia with 1:1 retrograde stimulation of the auricles. The lowest record is lead II after mild exercise. Note increase in rate of normal sinus rhythm and complete absence of paroxysms of tachycardia.

CASE 2.—*Short attacks of paroxysmal ventricular tachycardia with retrograde stimulation of the auricles disappearing after exercise; no other evidence of heart disease.*

C. W., a 12 year old boy, was admitted to the University Hospital as an outpatient on Jan. 4, 1937, because a routine physical examination two months before

31. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936, p. 60.

32. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, Springfield, Ill., Charles C. Thomas, Publisher, 1937, p. 272.

had disclosed a cardiac irregularity. He had had diphtheria as an infant and subsequently measles and chickenpox. At the age of 5 years he had had a severe infection of the respiratory tract complicated by mastoiditis necessitating operation. Tonsillectomy had been done soon thereafter without untoward event. He had had an allergic cutaneous disturbance in 1931 followed by hay fever and asthma. Sensitization cutaneous tests at that time were not helpful, and these difficulties ultimately cleared spontaneously. Two years prior to admission to the hospital, he had experienced vague pains in the lower extremities for a few months.

The patient had spent the summer of 1936 at a high altitude but had had an excellent endurance. On November 1 of that year, during a routine physical examination at a boarding school, an arrhythmia was discovered for the first time. It was present on repeated examinations. He had never complained of palpitation, dyspnea on exertion or ease of fatigue or, indeed, of any symptoms.

Physical Examination.—The patient was a normally developed and well nourished boy. The heart was not abnormal except for short attacks of tachycardia occurring at irregular intervals. There was no evidence of cardiac enlargement, and no murmurs were heard. The blood pressure was 120 systolic and 60 diastolic. Examination of the pulmonary fields disclosed a pleural friction rub over the entire left side of the chest posteriorly. There were no alterations in resonance, nor were any other adventitious sounds heard. Results of the remainder of the examination were entirely within normal limits.

Electrocardiographic Studies.—The electrocardiograms (fig. 5) showed short paroxysms of ventricular tachycardia with retrograde 1:1 stimulation of the auricles. All leads showed definite P waves superimposed on the T waves. There were also single ventricular extrasystoles having the same form as the QRS complexes of the runs of tachycardia. After exercise the extrasystoles became much less frequent, and the paroxysms of ventricular tachycardia entirely disappeared, only to return again after a period of rest.

Roentgen Examination.—Frontal stereoscopic and lateral projections of the thorax showed no evidence of pulmonary lesion. The cardiac and aortic shadows appeared normal.

DISCUSSION

Of the 7 definite cases of tachycardia of ventricular origin in childhood which are found in the literature, in 1 there was associated idiopathic cardiac hypertrophy and another was an instance of the Wolff-Parkinson-White syndrome. In the remaining 5 no definite cardiac diagnoses could be made, although 1 patient had clinical evidence of cardiac enlargement, another was thought to have myocardial disease on the basis of minor electrocardiographic changes over the course of five years and a third was suspected of having rheumatic heart disease. In the 10 reported cases of ventricular tachycardia in childhood in which the data are insufficient to meet the diagnostic criteria, 1 patient had rheumatic heart disease, 2 had myocardial changes of obscure origin and for the remaining 7 no cardiac diagnosis could be made. In adults, paroxysmal ventricular tachycardia has been observed in association

with nearly all types of heart disease [33] as well as in persons with no evidence of cardiac abnormality other than the bouts of rapid heart action.[34]

Although a few examples of supraventricular tachycardia associated with congenital cardiac anomalies have been recorded [35] and Faxén [36] reported that Bjerlöv had observed a case of paroxysmal tachycardia in a patient with bundle branch block and a congenital septal defect, a review of the literature has disclosed no instance of ventricular tachycardia occurring in a patient with congenital heart disease, and case 1 is believed to be the first recorded example of such an association. Inasmuch as this patient had an interventricular septal defect, it is interesting to note that in some instances of ventricular tachycardia occurring in patients with myocardial infarction the lesions were found to involve the septum.[37]

The second case of this report falls into the group of instances of paroxysmal ventricular tachycardia in children without signs of structural heart disease. In this respect the patient also resembles the majority of those patients in whom the ventricular tachycardia is induced by exertion or excitement, except that in this boy the arrhythmia was present when he was at rest and was abolished by exertion. Levy and Lewis [5a] were able to produce tachycardia of ventricular origin in cats under light chloroform anesthesia by the injection of small doses of epinephrine hydrochloride or by other forms of direct or reflex sympathetic stimulation. If unusual sensitivity to sympathetic stimulation had been the underlying mechanism in this case, the tachycardia should have become more firmly established after exercise. Since this was not true (fig. 5), this patient would appear to differ from the others. On

33. Schwensen, C.: Ventricular Tachycardia as the Result of the Administration of Digitalis, Heart **9**:199 (April) 1922. Arana, R., and Cossio, P.: Fibrilación auricular y taquicardia ventricular como eventualidad posible en el P-R corto con QRS ancho y mellado, Rev. argent. de cardiol. **5**:43 (March-April) 1938. Strauss.[6] Lundy and McLellan.[7]

34. Levine, S. A., and Fulton, M. N.: The Effect of Quinidine Sulfate on Ventricular Tachycardia: Clinical Observations, J. A. M. A. **92**:1162 (April 6) 1929. McMillan, T. M., and Bellet, S.: Ventricular Paroxysmal Tachycardia: Report of a Case in a Pregnant Girl of Sixteen Years with an Apparently Normal Heart, Am. Heart J. **7**:70 (Oct.) 1931. Footnote 11.

35. Russell, H. B., and Ellison, J. B.: A Case of Prolonged Tachycardia, Associated with Congenital Heart Disease, in a Child Fifteen Months Old, Lancet **2**:546 (Sept. 10) 1927. Werley, G.: Paroxysmal Tachycardia, with Ventricular Rate of 307, in a Child Four Days Old, Arch. Pediat. **42**:825 (Dec.) 1925.

36. Faxén, N.: Paroxysmal Tachycardia and Bundle Branch Block in a Boy of Eleven, Acta pædiat. **18**:491, 1936.

37. (*a*) Butterfield, H. G., and Hunt, G. H.: Observations on Paroxysmal Tachycardia, Quart. J. Med. **7**:209 (April) 1914. (*b*) Cossio, P.; Vivoli, D., and Caul, H.: Syphilis of the Interventricular Septum and Ventricular Tachycardia, Am. J. M. Sc. **194**:369 (Sept.) 1937.

the other hand, it is possible that under conditions of rest his heart was unusually susceptible to sympathetic stimulation and that exertion somehow abolished or counteracted this sensibility.

The chief symptoms which were present in previously reported cases of this arrhythmia in childhood were abdominal pain, dyspnea, nausea and vomiting, anorexia, irritability and pain in the chest. In 3 of the 7 definite cases in the literature, the patient showed evidence of congestive failure; included were the 2 cases with clearest evidence of structural heart disease. In the other 4 cases there were few abnormal conditions other than the rapid heart rate. The first patient here reported on presented all the complaints mentioned except pain in the chest. He showed definite evidence of heart failure during the tachycardia, but it is not unlikely that the congenital cardiac anomaly played some role in its development, for hepatomegaly was still present on reexamination three months after the cessation of the rapid heart action. Stewart and his co-workers [38] studied a man before, during and after ventricular tachycardia and found that during the abnormal rhythm there were decrease in cardiac output and vital capacity, a prolongation of the circulation time and a dilatation of the heart. The sudden occurrence and persistence of these alterations in J. B. (case 1), whose circulation was already embarrassed by the cardiac defects present, can well account for the degree of congestive failure which developed. In the second patient, however, the attacks of tachycardia were always of short duration, and, since his heart was otherwise normal, he could tolerate the rhythmic disturbance with ease, and indications of circulatory failure never appeared.

Quinidine has been recognized as the most efficacious drug in the treatment of paroxysmal ventricular tachycardia and has been given in tremendous doses in order to convert the cardiac rhythm to normal.[27b] This drug was used in 4 of the 7 previously reported cases of ventricular tachycardia in children.[38a] In 2 of them it was successful; apparently in the others the amount given was insufficient or the medication was not given long enough to be effective. It must be borne in mind when this drug is used that the excretion time is relatively rapid,[39] and to be successful one must often use doses of increasing size administered at frequent regular intervals. Unless this is done, a beneficial effect may not be obtained even from large doses. This was well shown in the case of the first child described in this report. The tachycardia had persisted

38. Stewart, H. J.; Deitrick, J. E.; Crane, N. F., and Thompson, W. P.: Studies of the Circulation in the Presence of Abnormal Cardiac Rhythms: Observations Relating to (Part I) Rhythms Associated with Rapid Ventricular Rate and to (Part II) Rhythms Associated with Slow Ventricular Rate, J. Clin. Investigation **17**:449 (July) 1938.

38a. Footnote 22 *c, d* and *e.*

39. Weisman, S. A.: Studies on the Time Required for the Elimination of Quinidine from the Heart and Other Organs, Am. Heart J. **20**:21 (July) 1940.

despite a total of 9.4 Gm. (140 grains) of quinidine sulfate given over a period of one week. Yet when the drug was given in hourly doses, increasing the size of the dose every five to six hours as the situation required until a total of 4.8 Gm. (72 grains) was administered within twenty-two hours, the desired result was effected.

In most of the previously reported examples of paroxysmal ventricular tachycardia in childhood, digitalis, mecholyl (acetylbetamethylcholine) or apomorphine was administered without any appreciable benefit.[40] Although these measures are frequently successful in cases of supraventricular tachycardia,[41] they are without effect on tachycardia of ventricular origin and are to be avoided. Herein lies the need for differentiating supraventricular and ventricular tachycardia, and it is therefore essential whenever a case of paroxysmal rapid heart action is encountered that careful clinical and electrocardiographic studies be made to determine the origin of the ectopic rhythm in order to permit selection of the proper mode of therapy.

SUMMARY

A review of the literature has disclosed 7 cases of paroxysmal ventricular tachycardia in childhood which satisfy the criteria necessary for this diagnosis. Two additional cases, recently observed in this clinic, are reported.

The first case was that of a child with congenital heart disease who had had ventricular tachycardia for two weeks. The paroxysm ceased only after a large amount of quinidine was given. For a few days thereafter the patient exhibited unusual forms of independent auricular and ventricular rhythms together with alterations in the form of the ventricular complexes.

The second case was that of a boy with no evidence of structural heart disease who had frequent, symptomless paroxysms of ventricular tachycardia of short duration. The arrhythmia disappeared on exertion.

Measures usually employed in the treatment of supraventricular tachycardia are without effect in ventricular tachycardia, and it is therefore essential to differentiate these two types of tachycardia whenever a case of paroxysmal rapid heart action of significant duration is encountered. Careful clinical and electrocardiographic studies should be made to determine whether the tachycardia is supraventricular or ventricular in origin, and if it is the latter quinidine sulfate should be given in adequate dosage to convert the rhythm to normal.

University of Michigan Medical School.

40. Footnote 22 *b*, *c*, *d* and *e*.

41. Walsh, B. J., and Sprague, H. B.: Paroxysmal Tachycardia in a Child, Treated with Acetyl-Beta-Methylcholine Chloride (Mecholyl), Am. Heart J. **20**: 111 (July) 1940. Hubbard.[21]

ECTODERMAL DYSPLASIA (ANHIDROTIC TYPE) WITH COMPLETE ANODONTIA

A SERIAL ROENTGENOGRAPHIC CEPHALOMETRIC APPRAISAL

ALLAN G. BRODIE, D.D.S., PH.D.
AND
BERNARD G. SARNAT, M.D.
CHICAGO

The importance of the deciduous and permanent teeth in the development of the face and jaws has been a controversial problem for a long time. One purpose of this investigation was to determine by serial roentgenograms of the skull the development of the face and jaws from the age of 1 year and 10 months to that of 5 years and 4 months in a patient with complete anodontia. A further purpose was to compare this development with the normal as to size, proportion and rate of growth. These particular aspects have been neglected in previous studies.

REVIEW OF LITERATURE

The literature contains a number of reviews of anodontia [1] and ectodermal dysplasia of the anhidrotic type, in which there is a lack of sweat and sebaceous glands, hair and teeth.[2]

The technic of assessing craniofacial development by serial roentgenograms has been described by Broadbent [3] and Brodie.[4] This method permits accurate positioning of the patient in relation to the film and the axis ray of the x-ray tube. The resulting roentgenograms are strictly comparable and permit the taking of accurate quantitative measurements through the use of either correctional scales or formulas.[5]

From the Department of Orthodontia and the Department of Histology, College of Dentistry, University of Illinois.

1. Werther, R., and Rothenberg, F.: Anodontia: A Review of Its Etiology with Presentation of a Case, Am. J. Orthodontics **25**:61, 1939.

2. Lord, L. W., and Wolfe, W. D.: Hereditary Ectodermal Dysplasia of the Anhidrotic Type (Congenital Ectodermal Defect), Arch. Dermat. & Syph. **38**: 893 (Dec.) 1938.

3. Broadbent, B. H.: A New X-Ray Technique and Its Application to Orthodontia, Angle Orthodontist **1**:45, 1931; The Face of the Normal Child, ibid. **7**:183, 1937.

4. Brodie, A. G.: On the Growth Pattern of the Human Head from the Third Month to the Eighth Year of Life, Am. J. Anat. **68**:209, 1941.

5. Adams, J. W.: Correction of Error in Cephalometric Roentgenograms, Angle Orthodontist **10**:3, 1940.

REPORT OF A CASE

E. Z., a white boy aged 1 year 9 months, was referred to us on May 18, 1938, because teeth had not appeared in the oral cavity.

The mother had no difficulty during pregnancy and delivered an apparently normal, full term 3,775 Gm. boy. The growth and development of the child during the neonatal and infancy periods were normal. He was given a diet consisting of breast milk (until 7 months), orange juice and cod liver oil under the direction of the physician.

Because the child had no teeth, when he was about 10 months of age the mother consulted a physician, who assured her the teeth would appear eventually. She was again assured on this point when the infant was 1 year 6 months of age. At 1 year 9 months the patient was referred to us after a physician had taken intraoral roentgenograms and found no evidence of tooth development.

Fig. 1.—Photographs of a 4 year old boy with ectodermal dysplasia. Note the sparse distribution of lanugo-like hair, the absence of eyebrows and eyelashes, the pronounced wrinkling of skin in the orbital area, the nasal ridge which does not appear to be prominent and the eversion of the lower lip. There are no teeth visible in the oral cavity.

The presence of eczema and lack of hair was noticed at 3 and at 6 months of age, respectively. The patient did not perspire, and it was necessary to apply cold wet packs in order to keep him cool on hot days.

The father and mother were of Polish descent and had no other children. Neither a parent nor any relative of the parents was known to have a condition similar to that of the patient.

Physical examination revealed a well developed and well nourished, mentally alert boy with albinoid, lanugo-like hair sparsely distributed over the scalp (fig. 1). The skin was dry and scaly. There were neither eyebrows nor eyelashes and no axillary hair. There were no pigmentary changes in the iris; the lens and the fundus of the eye were normal. The skin of the lower eyelid toward the inner canthus was hyperpigmented and strikingly wrinkled. Lacrimation was observed. The bridge of the nose seemed to lack its normal prominence. On

closure of the mouth the thickened lips pouted and gave the patient an aged appearance. Intraoral examination revealed the absence of teeth, firm mucosa over the jaws and no alveolar processes (fig. 1). The toe nails and finger nails were present and normal. The remainder of the physical examination revealed no abnormalities. After a complete anthropometric examination, the patient was reported to be within the lower limit of normal.[6]

The blood count and urine were normal. The Wassermann serologic reaction was negative. Examination of roentgenograms of the carpal bones taken when the patient was aged 4 years 5 months showed four and five centers of ossification in the right and left wrists respectively. Thus, according to present knowledge, carpal development was consistent with chronologic age. Microscopic examination of serial sections of skin obtained for biopsy from the right forearm failed to show the presence of sweat glands or sebaceous glands or of hair follicles. A

Fig. 2.—Lateral roentgenogram of the skull taken when the patient was aged 3 years and 4 months. Note the complete absence of teeth in both mandible and maxilla.

psychometric examination (revised Stanford-Binet, form L) at a chronologic age of 3 years and 11 months revealed a mental age of 5 years and an intelligence quotient of 128.

ROENTGENOGRAPHIC CEPHALOMETRIC APPRAISAL

Material.—Lateral roentgenograms of the skull were taken at six month intervals from 1 year 10 months to 5 years 4 months (fig. 2). This report is based on the study of head plates taken at 2 years 10 months, 3 years 10 months and 5 years 4 months.

6. The anthropometric examination was made by Dr. W. M. Krogman, of the departments of anthropology and anatomy of the University of Chicago.

The records of 20 normal white boys studied during a comparable period of growth were employed as controls. These were selected at random from the files of the Bolton Study at Western Reserve University.

Method.—All roentgenograms were analyzed in the same manner. Each was traced; the essential craniofacial landmarks were established (fig. 3), and linear and angular measurements were taken. The measurements tabulated have been found to be the most significant in studies on normal growth.

OBSERVATIONS

Examination of the head plates taken at 2 years 10 months, 3 years 10 months and 5 years 4 months, measurements taken from the tracings

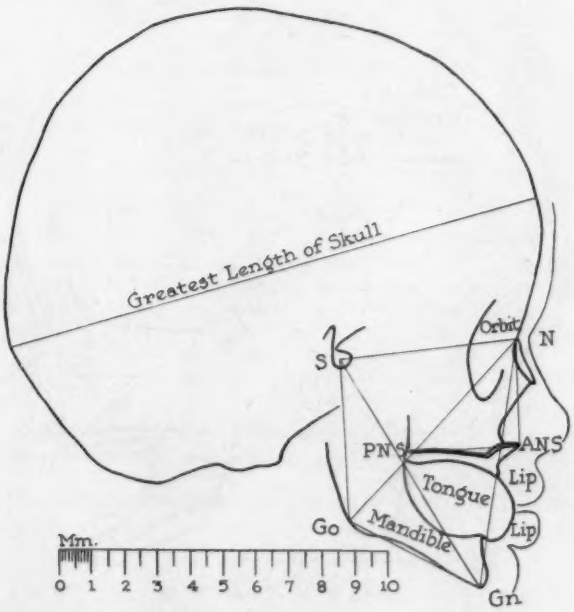

Fig. 3.—Craniofacial landmarks established for interpretation of the tracing of a lateral roentgenogram: (1) *Points: S,* center of sella turcica; *N,* nasion, junction of frontal and nasal bones; *ANS,* anterior nasal spine; *GN,* gnathion, bony chin point; *GO,* gonion, point at the angle of the jaw; *PNS,* posterior nasal spine. (2) *Lines: S-N,* center of sella turcica to nasion; *N-ANS,* nasion to tip of anterior nasal spine; *N-GN,* nasion to gnathion; *S-GO,* center of sella turcica to gonion; *ANS-PNS,* anterior to posterior nasal spine (taken as length of hard palate); *GO-GN,* gonion to gnathion (taken as length of lower border of mandible). (3) *Angles: S-N* and *ANS-PNS* (formed by posterior projection of these lines); *S-N* and *GO-GN* (formed by posterior projection of these lines); *S-N-ANS; S-N-GN; N-S-GN; N-S-GO; X-Y* axis (formed by the intersection of lines *N-GO* and *S-GN*).

(fig. 4) and their comparison with the normal controls (tables 1 and 2) permit the following statements:

1. Length of the cranium and of the cranial base are equivalent to a small normal.
2. All vertical and horizontal measurements of the face are less than small normal except the length of the lower border of the mandible, which is small normal.
3. All increments of growth show equality with small normal except that of palatal length.

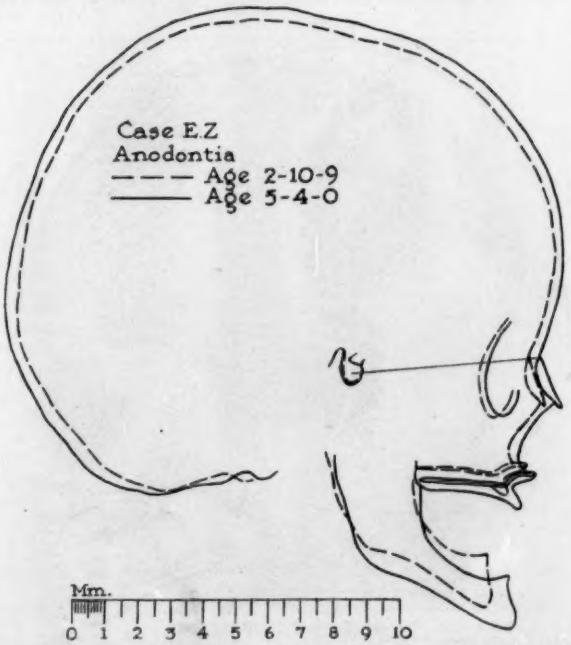

Fig. 4.—Superposition of tracings of lateral roentgenograms taken when the patient was aged 2 years 10 months and 5 years 4 months.

4. Vertical facial proportions are identical with normal proportions, the nasal height yielding 43 per cent of the total facial height.
5. There seems to be little disproportion between cranial and facial growth. The supraorbital region and the nasal bones appear to be normal.
6. The lips are everted, and the tongue occupies the entire oral cavity and flows out between the bony jaws, supporting the lips. This is typical of the infant before the eruption of teeth and of the adult after loss of the teeth.

7. The pattern of growth exhibits all of the phenomena of the normal pattern. The angular relations are close to the mean values of the controls, and as in the normal person these relations have a strong tendency to remain stable.
8. The alveolar processes are absent.

TABLE 1.—*Corrected Linear Craniofacial Measurements in Millimeters for Normal Children and Patient with Complete Anodontia*

	Controls at 3 Years of Age			Patient with Anodontia at 2 Yr. 10 Mo.	Comparative Measurements of Control with Smallest Measurements and Patient with Anodontia at Various Ages				Amount of Growth from 3 to 5½ Years	
	Maximum	Mean	Minimum		Control at 4 Yr.	Anodontia at 3 Yr. 10 Mo.	Control at 5 Yr. 6 Mo.	Anodontia at 5 Yr. 4 Mo.	Control	Anodontia
Greatest skull length	183	174	163	165	166	167.75	168.25	171.5	5.25	6.5
Sella to nasion	63.25	58.75	54.25	54	56	55.5	57	57	2.75	3
Nasion to anterior nasal spine	41	37.5	34	31.5	36	33	38	35	4	3.5
Nasion to gnathion	93	84.5	79	74.5	84	79	89	80.5	10	6
Nasion to gonion	93	84.5	78.75	73.5	83	76	86.75	79	7	5.5
Sella to gnathion	95.25	88.25	83	80.5	86.25	84.5	91	90	8	9.5
Sella to gonion	58	52.5	47	47.5	49	49.25	51.5	55	4.5	7.5
Length of palate	42	40.6	38.5	34	40.5	35	42.75	35.5	4.25	1.5
Length of mandibular border	54.5	50.5	45	44.5	46.5	47.25	49.5	49	4.5	4.5

TABLE 2.—*Corrected Angular Craniofacial Measurements in Degrees for Normal Children and Patient with Complete Anodontia*

Angle	Controls at 3 Yr., 4 Yr., 5 Yr. 6 Mo.			Patient with Anodontia at 2 Yr. 10 Mo., 3 Yr. 10 Mo., 5 Yr. 4 Mo.
	Maximum	Minimum	Mean	
S-N and ANS-PNS	13.5	2	8	5.25
S-N and GO-GN	40	27.5	35.5	33.0
S-N-ANS	92	79	85	84.5
S-N-GN	79	69	73	77.0
N-S-GN	72	62.5	67.5	63.42
N-S-GO	101.5	96.5	99.25	92.25
X-Y axis	120	106	111	104.5

COMMENT

Ectodermal dysplasia of the anhidrotic type is due, according to present views, to a gene mutation in the X chromosome, which is sex linked but not completely recessive.[7] This syndrome is rarely seen

7. Roberts, E.: The Inheritance of Anhidrosis Associated with Anodontia, J. A. M. A. **93**:277 (July 27) 1929. Thoma, K. H.: Oral Pathology: A Histological, Roentgenological, and Clinical Study of the Diseases of the Teeth,

(Footnote continued on next page)

in females. From the photographs in the literature a striking similarity of the patients is noted. In complete anodontia due to a gene mutation an ideal experiment has been created to determine the growth of the jaws in the absence of teeth.

In the light of present day concepts of the growth of the head, the data do not indicate that the presence or absence of teeth has any direct bearing on general facial development. It should be noted that the cranium and the body of the mandible have attained a small normal size while the middle part of the face is below this level. On the other hand, the rate of growth of all parts shows complete harmony with the normal. Thus this is not a matter of any deceleration of specific areas. How, then, can the differences be explained?

It should be recalled that sites of growth do not all appear simultaneously but rather develop in a definite and orderly sequence. Both embryologic and clinical observations indicate that the cranium is the first part to begin development. Following this comes the first branchial arch, from which is derived the middle part of the face, and then the mandible. Investigation has shown, further, that adverse constitutional factors can influence only those areas that are growing at the time of the disturbance but that they are not otherwise selective. That is, they tend to affect all parts equally. On the basis of this hypothesis one would reason that the etiologic factor in the case reported here had operated after the cranium had started to develop and while the middle part of the face was at its earliest and most rapid period of development. Recovery occurred before the mandible could be affected. In other words, a definite amount of critical time of growth had been subtracted from the developmental period of the middle part of the face, causing a disproportion. On this distorted pattern, normal increments of growth were added, and no further change one way or the other may be expected.

Many of the facial symptoms in cases of this type of ectodermal dysplasia are illusory. There is no doubt about the complete absence of the alveolar process, but this absence has not resulted in a loss of facial height, as might be implied from the sunken appearance of the mouth. Mandibular position is a result of muscle balance, and its position in this boy was no different than it would have been were all of the teeth present. This is indicated by the fact that the proportions within the facial area were strictly normal.

Patients with ectodermal dysplasia of the anhidrotic type are invariably described as presenting a broad and flattened nasal bridge.

Jaws and Mouth, St. Louis, C. V. Mosby Company, 1941. Lowenburg, H., and Grimes, E. L.: Ectodermal Dysplasia of the Anhidrotic Type, Am. J. Dis. Child. **63**:357 (Feb.) 1942.

With the pubertal development of the supraorbital ridges the impression of a sunken nose will probably become more pronounced. In examining the roentgenograms of the nasal bones, no pathologic alterations were noted, as might have been expected in congenital syphilis.[8] Their length was within normal limits although the width was not. This may account in part for the clinical appearance of the nasal bridge. On some persons in whom the deformity was conspicuous, surgical correction has been attempted.[9]

Systemic disturbances during the developmental period of the fetus or infant may be expressed in the growing tooth.[10] The tooth during its development passes through four stages:

Stage	*Dental Aberration*
1. Growth	
a. Initiation and Proliferation	— Anodontia
b. Morphodifferentiation	— Peg-shaped tooth; Hutchinson's incisor
c. Apposition	— Enamel hypoplasia
2. Calcification	
3. Eruption	— Pseudoanodontia
4. Attrition	

A disturbance of any of these stages accurately dates the time that the etiologic factor was active. Thus, anodontia represents a lack of initiation of dental development, which usually begins about the fifth week of intrauterine life. During the phase of differentiation the form of the tooth is determined. It is during this period that the peg-shaped tooth in partial anodontia and the Hutchinson incisor in congenital syphilis are formed.[10c] These should be carefully distinguished. A disturbance occurring during the time when the enamel-forming cells are active (apposition) is manifested clinically as enamel hypoplasia (chronologic enamel aplasia).[10b] Complete and partial anodontia should

8. Dr. M. J. Hubeny, of the roentgenologic department, Cook County Hospital, and Dr. A. Lewy of the Illinois Eye and Ear Infirmary, made these examinations.

9. Lewin, M. L.: Nasal Deformity in Anhidrotic Ectodermal Dysplasia, Arch. Otolaryng. **35**:210 (Jan.) 1942.

10. (*a*) Schour, I., and Massler, M.: Studies in Tooth Development: The Growth Pattern of Human Teeth, J. Am. Dent. A. **27**:1778 and 1918, 1940. (*b*) Sarnat, B. G., and Schour, I.: Enamel Hypoplasia (Chronologic Enamel Aplasia) in Relation to Systemic Disease: A Chronologic, Morpologic and Etiologic Classification, ibid. **28**:1989, 1941; **29**:67, 1942. (*c*) Sarnat, B. G.; Schour, I., and Heupel, R.: Roentgenographic Diagnosis of Congenital Syphilis, J. A. M. A. **116**:2745 (June 21) 1941.

also be differentiated from pseudoanodontia. In the latter condition the teeth have grown and calcified but have failed to erupt into the oral cavity.[11] This can be verified by roentgenograms of the jaws.

PROGNOSIS

Patients with these ectodermal defects have reached adult life, married and procreated. The intelligence, as in any group, has varied. The lack of hair is only a problem of esthetics and can be corrected by artificial means; artificial dentures have been supplied,[12] although the lack of teeth is no serious handicap in regard to adequate nourishment. The absence of sweat and sebaceous glands adds to the discomfort of the patient. Studies are to be conducted to determine how this may alter the patient's metabolism.

SUMMARY AND CONCLUSIONS

A case of ectodermal dysplasia of the anhidrotic type with complete anodontia has been presented. Serial roentgenographic appraisal of craniofacial development during childhood revealed the patient to be within the lower limits of normal and to be growing at a normal rate. This was further substantiated by anthropometric measurements and carpal bone assessments. The complete absence of teeth does not significantly impair development of the face and jaws.

808 South Wood Street.

11. Ivy, R. H.: A Case of Non-Eruption of Entire Permanent Dentition, Dent. Cosmos **75**:689, 1933.

12. Thoma, K. H., and Allen, F. W.: Anodontia in Ectodermal Dysplasia [case 38], Am. J. Orthodontics **26**:503, 1940.

Progress in Pediatrics

EARLY INFANTILE "DIFFUSE SCLEROSIS" OF THE BRAIN (KRABBE'S TYPE)

REPORT OF TWO CASES, WITH A REVIEW OF THE LITERATURE

GEORGE A. JERVIS, M.D.
THIELLS, N. Y.

Although published reports of diffuse sclerosis of the brain occurring in infancy and in childhood are not numerous, three types can already be recognized, which differ in age incidence, symptomatology and clinical course. The first type, described by Krabbe,[1] begins before the first year of age, shows a fairly rapid clinical course, of several months, and is characterized by muscular hypertonicity and tonic fits. The second type, first described by Scholz,[2] shows an age incidence between 3 and 10 years and a course extending usually over a period of a few years. Spastic paralysis, tremors, choreatic movements and epileptic attacks make up the clinical picture. Finally, a third type, described by Pelizaeus and later by Merzbacher,[3] begins in early infancy and runs a chronic course extending into adulthood.

The pathologic state of the brain underlying these different clinical types is essentially the same, its main features being diffuse destruction of myelin sheaths and consequent increase of glia tissue in the damaged regions. However, some histologic details may be mentioned as possible differential features: In Krabbe's type the axis-cylinders are severely involved and immature forms of glia are frequently encountered; in Scholz's type the fatty products of degeneration show some peculiarities of solubility and staining (so-called prelipids), and, finally, in the Pelizaeus-Merzbacher type characteristic perivascular islands of preserved myelin are observed.

It is the purpose of this presentation to report on a clinicopathologic study of 2 cases of the early infantile type of diffuse sclerosis. An

From the Research Department, Letchworth Village.

1. Krabbe, K.: A New Familial Infantile Form of Diffuse Brain Sclerosis, Brain **39**:74, 1916.

2. Scholz, W.: Klinische, pathologisch-anatomische und erbbiologische Untersuchungen bei familiärer diffuser Hirnsklerose im Kindesalter, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:651, 1925.

3. Merzbacher, L.: Eine eigenartige familiärhereditäre Erkrankungsform, Ztschr. f. d. ges. Neurol. u. Psychiat. **3**:1, 1910.

analysis of the symptoms and signs will indicate some characteristic features that may make possible the clinical recognition of the disease. In addition, the histologic examination will offer some data which may be of significance in the attempt to clarify the debated problem of the nature of the pathologic process.

REPORT OF CASES

CASE 1.—*History and Course.*—A. C., a Jewish girl aged 17 months, was admitted to Letchworth Village on March 1, 1940. Both parents were living and well. The father was 32 years old and the mother 28 years old at the birth of the patient. There was no consanguinity. No history of nervous or mental diseases in collaterals was obtained. The patient had only one sibling, who was apparently affected with a similar condition. This sibling, a girl, was examined only once, when 2 years of age. At that time she was physically a fairly well developed child, whose mental age was below the 6 month level. There was general hypertonicity of the limbs, which prevented any coordinate movements. The usual posture of the limbs was in extension, with trunk and head in slight opisthotonos. The deep reflexes were normal; there was no Babinski sign. Some dystonic movements were noted in the muscles of the tongue and the fingers. There was bilateral nystagmus. The pupils reacted normally. The condition dated from the first months of life, the first symptoms having occurred at about 5 months, and had been slowly progressive. No further data concerning this patient could be obtained.

The patient under study was born after an uneventful gestation. Delivery was at term, but the labor was difficult and forceps were used. However, no signs of cerebral injury were noted by the physicians in charge. The child developed regularly until the fourth month of life, behaving in every respect as a normal infant. It was noted then that she appeared listless and less playful than usual. Two months later, mental retardation becoming more apparent, an encephalogram was made. This showed dilatation of the cisterna pontis and of the occipital horns of the lateral ventricles. A neurologic examination showed increased tonus in the lower extremities and hyperactivity of both knee and ankle jerks. The mental retardation became progressively more severe, and at 1 year of age the patient attained an intelligence quotient of 13 on the Gesell test for infants. The spasticity also increased. Tonic fits were frequently observed, during which the whole body became rigid, generally in extension. These attacks were induced by a variety of stimuli, such as rough handling of the child or a sudden noise, and were accompanied by a great deal of crying, as if the fits were painful.

On examination at admission, the patient appeared as a fairly well nourished child of a size corresponding to her age. She lay in bed in a characteristic posture, the head hyperextended, the legs extended and often crossed in a scissors-like fashion, the feet in plantar extension, the arms at times in extension and at other times bent at the elbow and the fingers tightly clenched. On passive manipulation of the head and limbs, the muscles appeared hypertonic, and considerable effort was necessary to put the head or the legs in flexion. The muscular stiffness was so pronounced that it was possible to lift the child by holding her with one hand on her back without altering the posture of the head and limbs. Deep reflexes could not be elicited. The sign of Babinski

was present bilaterally. Some modification of the posture of the limbs was obtained by rotation of the head, but these cervical reflexes were inconstant, and often their occurrence was disturbed by the appearance of tonic fits resulting from the manipulation of the head. These fits were characterized by a sudden exaggeration of the hyperextension and were accompanied by screaming. A dolorific stimulus, such as pinching the skin, produced an attack, while acoustic or visual stimuli were ineffective. Tonic fits occurred also spontaneously. Clonic movements were not observed.

The pupils reacted but sluggishly to light. They varied considerably in size from one moment to another. There were slow continuous movements of laterality in both bulbi. Ophthalmologic examination showed paleness of the disks and contracted blood vessels. The retinas were normal, and the maculae luteae showed no alteration.

Mentally, the patient appeared to be on a purely vegetative level.

Routine laboratory examination, including tests of blood and spinal fluid, gave normal results.

The course in the hospital was rapid; a temperature of 102 F. developed on the first day, which rapidly increased to reach 107 F. on the third day, when the patient died. During the last day the tonic fits became so frequent that they appeared almost continuous.

Necropsy.—Postmortem examination was performed eight hours after death. Examination of the viscera showed little of significance beyond a few scattered foci of recent bronchopneumonia in the right lung.

The brain appeared large, weighing 1,350 Gm. On external examination the main patterns were easily recognizable and showed no significant deviation from the normal. The white matter of the centrum semiovale appeared grossly soft, almost gelatinous in consistency, while the cortical gray matter was normal. Demarcation between gray and white matter was sharp. No internal hydrocephalus was observed.

Histologic examination was performed as follows: large blocks, including the whole hemisphere in the region of the frontal, parietal, temporal and occipital lobes, were fixed in alcohol, embedded in celloidin (a pyroxylin preparation) and stained by the following methods: Nissl for cells, Weil for myelin, Holzer for glia and Gross for axis-cylinders. Blocks from several cortical regions and basal ganglions were fixed in formaldehyde-bromide solution and stained by Cajal's and Hortega's methods. The other parts of the brain were fixed in solution of formaldehyde, and blocks from representative regions were stained with a variety of methods, including use of sudan III, sudan black, scarlet red and osmic acid for fatty material and Spielmeyer's method for myelin, Bodian's for neurofibrils and Alzheimer's for glia.

White Matter: The most striking alteration was observed in the myelin preparations. As seen in figure 1, the whole white matter of the centrum semiovale contained no myelin detectable with the usual hematoxylin methods, even when differentiation was interrupted at an early stage in which the gray matter retained the stain. This absence of myelin was complete, involving also the subsulcine fibers and the myelin sheaths of the cerebral cortex. At high power no intact sheaths were seen but only a few granular fragments, which stained palely with hematoxylin. In the capsula interna numerous myelinated fibers could be observed, which, however, showed various alterations, such as circumscribed swellings and partial fragmentation, when observed at high power. Several fibers irradiating from the capsula interna toward the central convolu-

tion appeared also partially myelinated. The capsula externa contained some myelin, while the capsula extrema was entirely demyelinated. The corpus callosum, commissura anterior and chiasma opticum were likewise demyelinated. Myelin was not observed in the fibers of the corpus striatum or the thalamus. In the pons the transverse fibers were remarkably well preserved. Of the

Fig. 1 (case 1).—Frontal sections of the hemisphere, showing extensive demyelination. Weigert's stain (differentiation was interrupted at an early stage, so that the gray matter is partially stained).

longitudinal fibers, the rubrospinal tract appeared partially demyelinated, while the other tracts, including the pyramids, were myelinated but the myelin was remarkably pale when compared with normal preparations.

Silver stains of the demyelinated areas showed a considerable destruction of axis-cylinders. The remaining axons were altered, showing unevenness of color

and caliber, varicosities and fragmentation. In the capsula interna the axons appeared better preserved.

Cellular stains of the demyelinated areas brought out various cellular elements. These included: (*a*) Numerous gitter cells of the usual type, showing reticulated cytoplasm and a small eccentric nucleus. With methods for fat, the cytoplasm was seen to contain fatty material, which stained bright red with scarlet red and sudan III, black with osmic acid and sudan black and pale brownish with hematoxylin. This material was readily dissolved in the usual

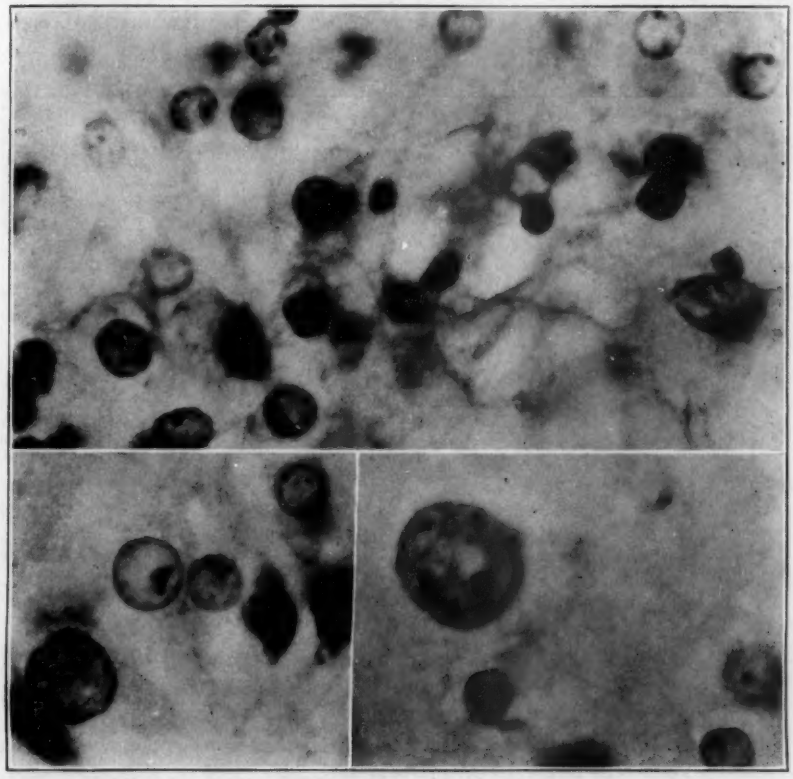

Fig. 2 (case 1).—Peculiar glia nuclei as described in the text. Nissl stain.

solvents of fats, including acetone, ether, benzene, chloroform and xylene. Cells of this type were demonstrable with a variety of methods but particularly well with Hortega's silver impregnation. (*b*) Large neuroglia cells clearly brought out by Cajal's method, showing abundant cytoplasm, numerous dendrites and a large nucleus. These cells were not numerous, being present only in certain areas. (*c*) Small glia nuclei, some of which exhibited characteristics of the oligodenroglia nuclei in the Nissl preparation while others were similar in character to the small cells found in the germinative centers at an earlier stage of life. (*d*) Large pale naked glia nuclei identical with those found in the cortex and described later.

Gray Matter: Nissl preparation of the various cytoarchitectural fields of the cerebral cortex showed little alteration in the normal cellular lamination. In the frontal fields the various cellular layers were remarkably well preserved, but there was an almost complete disappearance of myelin sheaths, and the axis-cylinders appeared diminished in number and showed frequent alteration. In the parietal regions the neuron cells were also well preserved, and the Betz elements stood out prominently. Myelin sheaths were not seen. In the temporal areas there was some involvement of the third layer, as evidenced by cellular rarefaction. In the occipital regions the calcarine cortex showed the typical eight layer distribution, and there were several well developed stellate cells of Meynert.

The striking change found in the gray matter of the cortex was the presence of numerous large nuclei apparently of glial origin (fig. 2). These were round

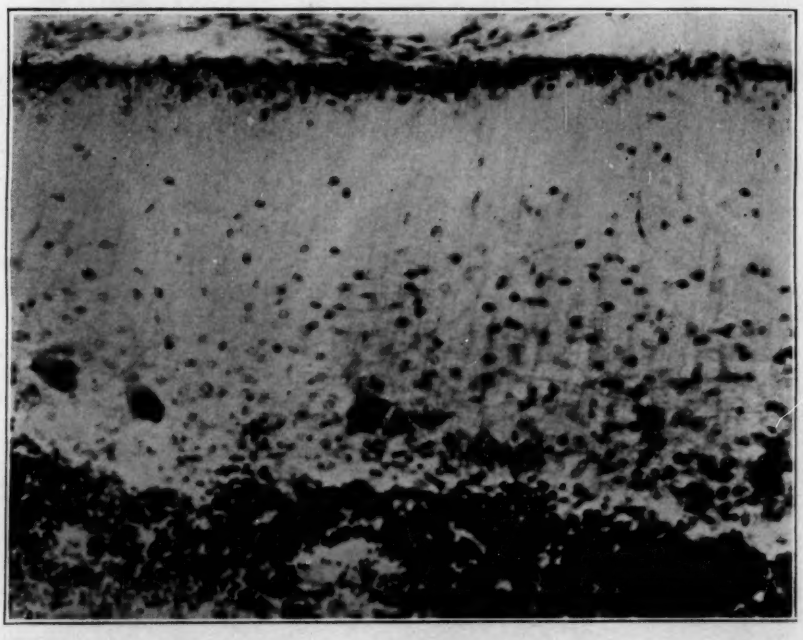

Fig. 3 (case 1).—Cerebellar cortex in the Nissl preparation, showing lesions of the Purkinje cells and external granular layer.

or, less frequently, elliptic in shape, varying in size from that of a medium-sized pyramidal cell to two or three times as large; they were pale in color except for a darkly stained cellular membrane; there were a few granules of chromatin located generally near the cellular membrane; one or two of the larger granules often exhibited a reddish tinge in the Nissl preparation. There were neither dendrites nor cytoplasm to be seen with the numerous methods employed. These large pale nuclei were numerous in all layers of the cortex and throughout all the regions, being at times isolated and at other times in clusters of three or four elements. Groups of such nuclei were constantly observed in the molecular layer, especially in the external part of it, where they often formed what appeared to be a veritable cellular layer. Another characteristic of the gray matter was the

almost complete absence of oligodendroglia, as seen in both Nissl and Hortega preparations. The microglia of the cortex showed no significant changes.

The gray matter of the basal nuclei, thalamus, hypothalamic nuclei, pons and medulla showed no alteration as far as the nerve cells were concerned. Here also large pale nuclei of glia were frequently observed.

Cellular nests were observed in the region surrounding the occipital horns of the lateral ventricles. These consisted of two main types of cells; the first was made up of small dark round nuclei with little or no cytoplasm and with numerous chromatin granules; the second type was similar to the large glia nuclei found in the cortex. These cellular nests bore similarities to the germinative centers which are found in earlier periods of development.

In the cerebellum (fig. 3) the molecular layer was abnormally wide, and its external part contained a cellular layer consisting of four or five rows of small darkly stained nuclei. Numerous large pale glia nuclei of the type previously described were present in the molecular layer, especially in the Purkinje layer. Numerous Purkinje cells had disappeared, and the remaining ones showed sclerotic changes. The granular layer had a spongy appearance. The medullary substance was demyelinated.

CASE 2.—*History and Course.*—H. S., a Jewish boy aged 2 years and 9 months, was admitted to Letchworth Village on Oct. 25, 1940. The family history showed nothing of significance except consanguinity. The grandparents were all living and in good health. The paternal grandfather was a first cousin of the maternal grandfather, their mothers having been sisters. Both parents were also in good health. The father was 36 years of age and the mother 26 years at the time of the birth of the patient. There was no other sibling.

The mother had a normal gestation period. Labor was normal in every respect. The weight of the patient at birth was 8 pounds. For the first four months of life the patient's behavior was that of a normal child; at 4 months he was able to hold his head in an erect position and would follow a light. After the fourth month, without apparent cause, a change was noted: He appeared listless and apathetic, and had difficulty in holding up his head. About the same time some muscular hypertonicity was noted. The patient used to cry a good deal, and while crying, stiffening of the whole body in extension was observed. Shortly after, it was noted that the slightest noise would produce an attack of generalized hypertonicity, in which the body was in opisthotonos and the limbs were held in forced extension. At 8 months, he was seen by a prominent neurologist, who suggested the diagnosis of amaurotic familial idiocy although no macular lesions were to be observed. At 1 year the patient had pneumonia, after which the neurologic syndrome appeared improved. Shortly after, however, hypertonicity and tonic fits recurred, the latter becoming more and more frequent. Mental deterioration also steadily progressed. On several occasions the patient was observed to have a high temperature without apparent cause.

On admission, the patient appeared as a fairly well developed and well nourished child. He lay in the bed with his head slightly retracted, his arms somewhat bent at the elbows, his hands clenched and his legs and feet stiffly extended. When moved from this posture he would whine. Considerable hypertonicity was found on passive manipulations of the limbs. The deep reflexes were difficult to elicit, but when a response was obtained it seemed to be within normal range. The plantar response was bilaterally in extension. The abdominal reflexes were absent. Both pupils were dilated and reacted sluggishly to light; in the lateral position of the bulbi nystagmus could be occasionally noted. The optic disks were

pale, with well defined borders, and the vessels were narrower than normal. There was no abnormality of the macula. Mentally, the patient appeared to be at the level of low grade idiocy; he showed no signs of visual recognition or of auditory sensation. His only utterance was a frequently elicited whining.

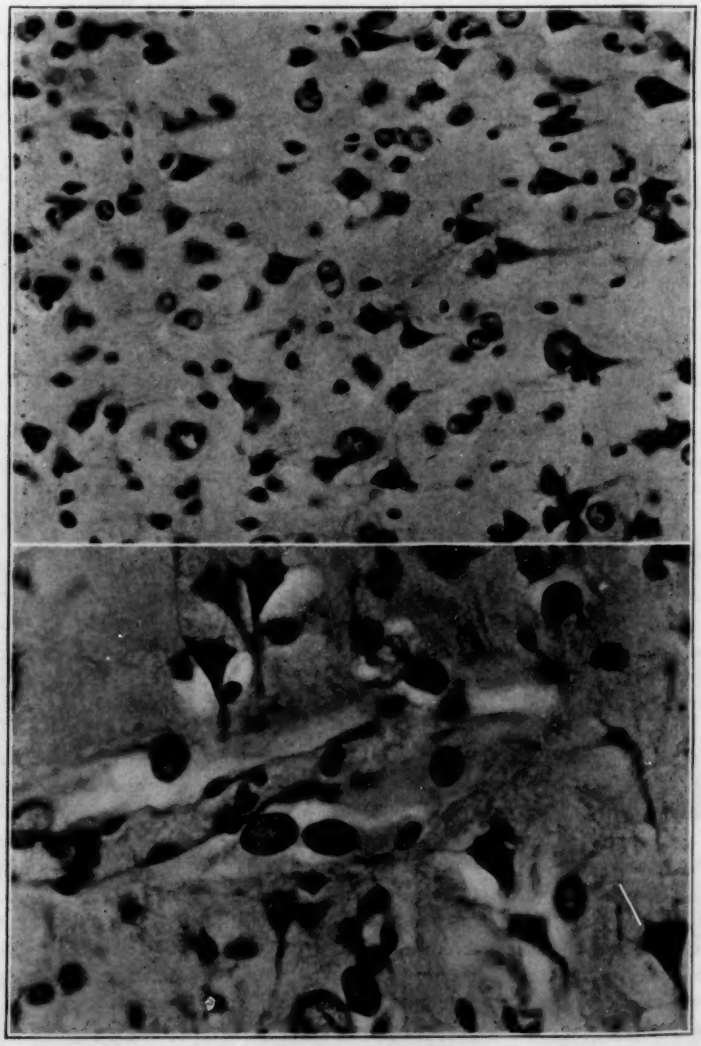

Fig. 4 (case 2).—Peculiar large nuclei in the cerebral cortex. Nissl stain.

Systemic examination revealed no abnormalities. Routine laboratory tests, including repeated examinations of the spinal fluid, gave normal results.

The course in the hospital was characterized by a long succession of tonic fits, during which the patient was in opisthotonos, with the legs hyperextended

and the arms slightly flexed at the elbow. The fit generally lasted a few minutes and was often accompanied by cyanosis. Several fits within a one hour period were often observed. Occasionally, clonic movements of little amplitude occurred during a tonic fit. During the intervals the clinical picture remained the same as that already described. Tube feeding was necessary, since the patient was unable to swallow. For over two months high temperature was present; the graph showed almost daily peaks of 105 to 107 F. Repeated examinations, including taking of several roentgenograms of the chest, failed to demonstrate any apparent cause of the hyperthermia.

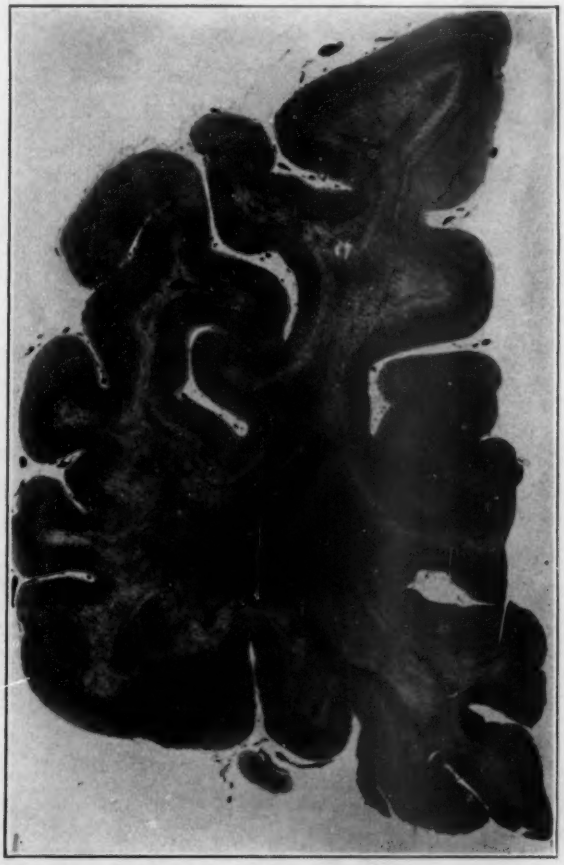

Fig. 5 (case 2).—Section of the frontal lobe, showing the extension of the demyelination. Weil stain.

The patient died on December 5, at the age of 2 years and 10 months.

Necropsy.—Postmortem examination was limited to the brain. The skull was of normal thickness. External gross examination of the brain, which weighed 960 Gm., failed to show any significant abnormality. The brain was cut in coronal slices, and on the cut surface the texture of the white matter of the centrum

semiovale varied in different areas, appearing soft and friable in the frontal lobes while in the occipital lobe it was hard and the tissue seemed shrunken. Demarcation between the gray and the white matter was everywhere clearcut. There was no dilatation of the frontal and temporal horns of the lateral ventricles, while the occipital horns appeared somewhat dilated.

Fig. 6 (case 2).—Section of the parietal and temporal lobes, showing the distribution of the demyelination. Weil stain.

Histologic examination was performed, the methods as indicated in case 1 being used.

The cerebral cortex as seen in the Nissl preparation showed some loss of neurons diffusely distributed throughout various fields and involving particularly the large pyramidal cells of the third and fifth layers. In addition, the remaining neurons were often shrunken and distorted. However, the normal lamination was

not much disturbed, and the cortical cellular layers were everywhere recognizable. As in case 1, the cortical gray matter contained a great number of large pale glia nuclei identical in their structure and staining properties to those described in case 1 (fig. 4) except that they were more numerous and oftener showed a

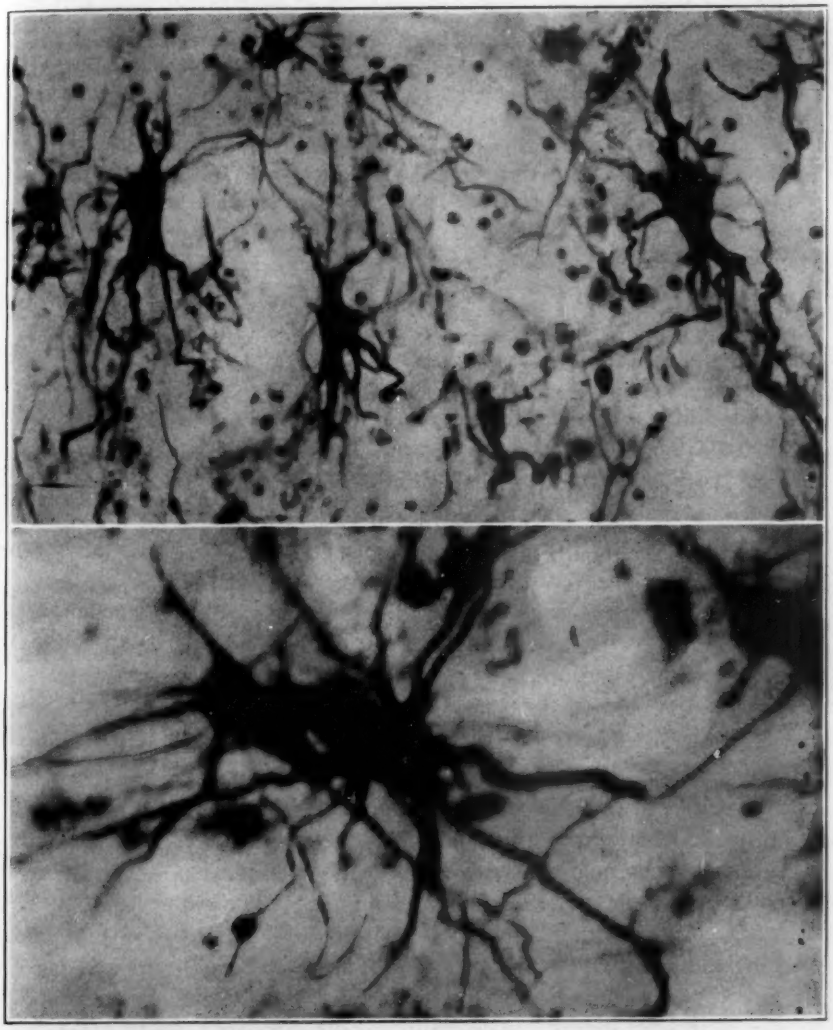

Fig. 7 (case 2).—Section showing giant astrocytes as found in the sclerotic areas. Cajal method.

tendency to perivascular arrangement. Oligogliacytes were present but in lesser number than in normal brains. The microglia showed no significant alteration in these regions. Numerous large pale glia nuclei were found also in the gray matter of the basal ganglia and the thalamus, while in these regions the neurocellular alterations were less conspicuous than in the cortex.

As in case 1, the most striking alteration was found in the white matter of the centrum semiovale, as seen in the myelin preparation. An extensive demyelinating process was present throughout. The destruction of myelin was complete in the occipital lobe, where no trace of stainable sheaths was observed; in the frontal lobe the process spared the central part of the centrum semiovale, which appeared incompletely stained (fig. 5), and involved only partially the subsulcine fibers. In the temporal and parietal lobes small areas of preserved myelin were also observed (fig. 6), which showed no relation to blood vessels. Moreover, the fibers of the capsula interna were partly myelinated (fig. 6). On high power examination, these areas of preserved myelin showed considerable alteration of the sheaths, which appeared thinner and paler than normal. A dustlike fragmentation of the sheath was common, while swellings were not observed. Bodian preparations of the demyelinated regions showed destruction of axis-cylinders in the areas of complete demyelination; little alteration was found in the regions of partial demyelination.

The cellular content of the demyelinated areas showed the same characteristics seen in case 1. However, gitter cells were not so numerous and in certain regions were entirely absent, while large neuroglia cells exhibiting numerous dendrites were more numerous than in case 1 (fig. 7). Glia fibrils, as demonstrated by the Holzer stain, were also more abundant. The peculiar large pale glia nuclei already described were especially numerous in the white matter of the frontal lobe.

The cerebellum was considerably altered. The white matter of the medullary center was demyelinated, and the granular layer contained less granules than normal; the Purkinje cells were conspicuously diminished in number and showed disturbances in arrangement, some cells being situated in the external part of the molecular layer. An external granular layer similar to that described in case 1 was observed, and numerous large pale glia nuclei were scattered throughout the molecular layer.

COMMENT

A survey of the literature shows that a few other cases similar in symptoms and pathologic changes to those here described have been reported. A brief review of these cases may be pertinent at this point.

Krabbe [1] in 1916 reported 5 cases. In case 1, that of a boy, the first manifestations of the disease occurred at the age of 5 months, with "fits of stiffness" of all extremities and mental retardation. On examination two months later, generalized hypertonicity in extension was observed together with tonic and occasionally clonic fits. The patient died at 13 months. Postmortem examination showed destruction of myelin and axis-cylinders diffuse to the cerebral hemispheres, midbrain and cerebellum. A large number of glia cells were found in the degenerated areas. Fat was scanty. The neuron cells appeared well preserved. The patient in case 2, a girl sibling of the patient in case 1, showed essentially the same symptomatology. The onset was at 4 months, although some stiffness might have been present earlier, and the patient died at 12 months of age. The pathologic specimen showed the same picture as that of case 1, but fatty substances were more numerous. Cases 3 and 4, in 2 sisters, showed a similar clinical picture: onset at the

fifth month, with stiffness in extension and opisthotonos which steadily progressed until the end, and frequent periods of elevated temperature. Death followed at 9 months in case 3 and at 18 months in case 4. The brain of the former patient was not examined histologically; that of the latter showed a pathologic state similar to that in case 2. Krabbe's case 4 concerned a boy who at the age of 5 months showed mental retardation and muscular rigidity. These symptoms progressed till death, which occurred at the age of 11½ months. The brain was grossly atrophic and hard in consistency. Histologic examination was not performed.

Globus and Strauss [4] reported 3 cases which can be considered instances of early infantile diffuse sclerosis. The first case was that of a boy who began to have convulsive seizures at the age of 5 months, after acute gastrointestinal disturbances. Later generalized rigidity, opisthotonos, bilateral atrophy of the optic nerve and pronounced wasting were observed. Death occurred at 13 months. Post mortem, there was extensive loss of myelin and axis-cylinders in the white matter of the brain, with infiltration of compound granular cells and diffuse hyperplasia of fibroblastic astrocytes. The gray matter appeared intact. The patient in the second case, a girl, was admitted to the hospital at 9 months of age because of mental retardation, the onset of which could not be definitely established. Spasticity developed rapidly, together with severe convulsive seizures, and the patient died sixteen days after admission. The pathologic changes were substantially the same as in the previous case, except for the fact that the gliosis was less intense. In the third case, repeated generalized convulsions with fever developed in a girl at the age of 6½ months. Two days later she was admitted to the hospital, where generalized rigidity was observed. The child died four days after the onset of the illness. The pathologic changes were, in the main, the same as in the previous cases. The process was, however, of a more acute and destructive character. The alterations of the glia were mainly of a regressive nature.

Russell and Tallerman [5] reported the case of a girl, who at the age of 4 months showed lack of activity and some stiffness of the limbs. Two months later, there were idiocy and pronounced rigidity of the arms and legs. Cervical reflexes were present. The child died at 7 months of age. Post mortem, there was widespread degeneration affecting the cerebral and cerebellar white matter, accompanied by a marked microglia reaction and an uneven gliosis. The axis-cylinders were diminished in number. The cortical neuron cells were degenerated in the depths of the

4. Globus, J. H., and Strauss, I.: Progressive Degenerative Subcortical Encephalopathy, Arch. Neurol. & Psychiat. **20**:1190 (Dec.) 1928.

5. Russell, D. S., and Tallerman, K. H.: Familial Progressive Diffuse Cerebral Sclerosis of Infants, Arch. Dis. Childhood **12**:71, 1937.

sulci, while they were well preserved at the summits of the convolutions. A sibling of this patient, a boy, began to suffer from convulsions and spasticity of the legs at the age of 4 weeks and died a few days later. Autopsy was not performed.

The cases described by Eiselsberg [6] concerned 2 sibs. The first, a boy, showed at the age of 4 months generalized muscular rigidity and tonic fits. One month later, there were idiocy, tonic-clonic fits and high temperature. After a transitory improvement the same symptom complex appeared, and the child died at 7½ months of age. The autopsy showed diffuse demyelination with abundant fatty-like products and glia reaction. The second patient, also a boy, showed likewise mental deficiency and tonic-clonic fits with opisthotonos at the age of 4 months. He died at 5½ months. Histologic examination of the brain was not performed.

The case reported by Canavan [7] concerned a boy who died at 16 months of age. The onset of the disease could not be ascertained; the main symptoms were mental defect, increase of reflexes and nystagmus. The brain was enlarged and soft. There were a subcortical loss of myelin and a diffuse and severe edema of the white matter.

The family reported by de Lange [8] included 4 siblings affected with the disease. The first, a girl, at about 4 months of age showed mental defect and increasing muscular stiffness. Death occurred at the age of 8 months. Autopsy was not performed. The second, a girl, developed normally until the age of 6 months, when some muscular stiffness was noted. At 8 months, general muscular hypertonicity was well established and tonic fits were observed to be brought about by a variety of stimuli. The hypertonic syndrome progressed in intensity, and death followed at the age of 13½ months. Post mortem there was an extensive destruction of myelin sheaths and to a less extent of axis-cylinders. Little lipid material was observed. The glia was everywhere affected: hypertrophic and hyperplastic adult macroglia was observed, together with immature forms of glia. The third sibling, a twin of the patient of case 2, was admitted to the hospital at the age of 9 months, showing symptoms identical with those of her twin. This patient died at the age of 2 years and 7 months. Autopsy was not performed. Finally, a fourth member of this family, a boy, was observed at the age of 8 months, when he showed mental defect and hypertonicity. He died at the age of 15

6. Eiselsberg, F.: Ueber frühkindliche familiäre diffuse Hirnsklerose, Ztschr. f. Kinderh. **58**:702, 1937.

7. Canavan, M. M.: Schilder's Encephalitis Periaxialis Diffusa: Report of a Case in a Child Aged Sixteen and One-Half Months, Arch. Neurol. & Psychiat. **25**:299 (Feb.) 1931.

8. de Lange, C.: Ueber die familiäre infantile Form der diffusen Gehirnsklerose (Krabbe), Ann. pædiat. **154**:140, 1940.

months, and the pathologic examination showed lesions similar in nature and distribution to those of case 2.

There are, in conclusion, in the available medical literature, 12 histologically verified cases of early infantile diffuse sclerosis. To these the 2 cases here described should be added. In 4 other cases the diagnosis was not verified histologically but was made on clinical grounds and on the fact that the patients were siblings of patients who had been examined post mortem.

From the examination of these cases, some significantly uniform clinical and pathologic features become apparent. The disease is familial; in fact, in 18 instances in thirteen studies 2 or more siblings were affected. Moreover, in the nonfamilial cases, 2 patients had no siblings (Globus and Strauss,[4] and present case 1) and 2 others had only 1 sibling (Globus and Strauss [4]); hence in these instances no definite conclusion as to familial character can be reached. Only 1 case remains (Krabbe's case 5) in which several siblings (the number is not stated) were said to be normal. The fact that the disease appears suddenly among siblings of healthy parents, all the other members of the family being normal, and the presence of consanguinity in at least two families (Russell [5] and present case 2) suggest that some rare recessive gene may be responsible for the occurrence of the disease.

The clinical symptoms and the course of the disease appear characteristically similar in almost every instance. The patients develop normally until the age of 4 to 6 months, when the first manifestations of the disease set in, often abruptly. These consist of mental retardation and muscular hypertonicity. The progression of these symptoms is rapid: In a few months there is complete idiocy accompanied by generalized hypertonicity, the trunk and head being in opisthotonos, the legs in forced extension and often crossed in scissors-like fashion, the arms extended or slightly flexed at the elbow and the hands tightly clenched or in tetanic position. At this stage, tonic fits are extremely frequent, being characterized by a sudden spastic accentuation of the hyperextended posture brought about by a variety of stimuli and lasting from a few seconds to several minutes. In case 2, tonic fits were almost continuous for a period of several weeks. True epileptic seizures, although frequently recorded in the cases reported on by Globus and Strauss,[4] have been rarely encountered in the other patients of this series. Manifestations of decerebrate rigidity have been repeatedly observed, together with grasping and similar pathologic reflexes. The deep reflexes are often difficult to obtain because of muscular stiffness but show no important deviation. Atrophy of the optic nerve is frequently mentioned and was present in 2 cases here described. In Krabbe's [1] and Eiselsberg's [6] cases and in the present case 2, high

temperature was observed, as shown in figure 11 of Krabbe's report. Since no apparent cause was found, Krabbe [1] ascribed it to alterations of the centers regulating the temperature or to the action of products of destruction of the central nervous system.

The course of the disease is rapid, averaging four to eight months. One of Globus and Strauss's [4] patients died within a few days, while examples of most protracted course are de Lange's [8] case 4 and the present case 2, in which the disease was of over two years' duration. The course is progressive, although some temporary improvement may occasionally occur, as evidenced by Eiselsberg's [6] case and by the present case 2. In conclusion, as de Lange [8] pointed out, while in other types of diffuse sclerosis the clinical manifestations are protean and the diagnosis difficult, in the Krabbe type the clinical picture is uniform and characteristic enough to make it possible to recognize the disease in the absence of postmortem observations. To be sure, infantile amaurotic familial idiocy shows a similar clinical picture but can be differentiated by the presence of macular changes.

The pathologic picture presents also considerable uniformity throughout the whole series of cases. Demyelination is always extensive and is accompanied by pronounced destruction of the axis-cylinders, as shown in the present 2 cases and in Krabbe's,[1] Globus and Strauss's [4] and Russell and Tallerman's [5] cases. Variations exist as to the cellular content of the demyelinated areas, gitter cells prevailing in some cases and dense gliosis in others. The former occurrence was well exemplified in case 1; the latter, in case 2. However, these differences are hardly significant, being apparently due to the age of the pathologic process. Involvement of the gray matter is mentioned only in Russell's [5] case, while usually there is no alteration (as in case 1) or diffuse mild cellular loss (as in case 2). In every instance the blood vessels are essentially normal, and perivascular infiltration with hematogenous elements is generally lacking. The cerebellum is usually involved, as it was in the cases here described. The presence of a superficial granular layer, which was found in both cases of the present report and also in Russell's [5] case, is to be interpreted as a retarded development, this layer being present in earlier stages of development.

The presence of peculiar glia elements beside reactive types of glia was a prominent feature of the pathologic picture in both cases here described. The large pale nuclei of glia which were found throughout offer some difficulty of interpretation. They differ from *gemästete* cells mainly by the absence of cytoplasm. Some similarities were found to the glia cells described by Alzheimer in Wilson's disease; however, the indentations and lobulations characteristic of this type of nuclei were lacking. Morphologically the cells bore close similarities to those found

in earlier stages of development by Roback and Scherer.[9] These authors have demonstrated that during the eighth month of intrauterine life the most frequent glia elements to be found in both gray and white matter are large pale glia nuclei, which gradually disappear during the first months of extrauterine life. In addition, during the period of prevalence of these glia cells, oligogliacytes are scanty, a condition which was noted in the present cases. The large glia nuclei can be considered with good justification, in conclusion, as immature forms. It should be noted that Krabbe [1] himself and more particularly de Lange [8] observed in their cases the frequent occurrence of abnormal glia, embryonic in character.

These histologic observations may offer some clue as to the nature of the pathologic process. Although considerable doubt still exists concerning the mechanism of myelin destruction in diffuse sclerosis, two major hypotheses present themselves for consideration. The first maintains that toxic substances of exogenous or endogenous origin act on the myelin either directly or indirectly by way of vascular lesions and bring about a destruction of sheaths. Considerable evidence in favor of this hypothesis is offered by the occurrence of demyelination in animals experimentally intoxicated with various substances and by the observation of diffuse sclerosis in human beings during some intoxications.[10] It should be noted, however, that the pathologic picture in these cases is that of destruction of myelin accompanied by mere reactive aspects of the glia (formation of scavenging cells and hypertrophy-hyperplasia of the macroglia), whereas the peculiar types of glia observed in cases of Krabbe's disease are absent.

According to a second hypothesis, a primary involvement of the glia is responsible for the lesion of the myelin. Thus Collier and Greenfield [11] first suggested that the disease is due to a lesion of those cells which have to do with the nutrition of the myelin sheaths. Scholz [12] likewise stated that the fundamental lesion is to be found in a hereditary anomaly of the capacity of the glia to regulate the metabolism of myelin. According to Levaditi [13] there is a disturbance of lipid metabolism due to an "inver-

9. Roback, H. N., and Scherer, H. J.: Ueber die feinere Morphologie des frühkindlichen Gehirns unter besonderer Berücksichtigung der Gliaentwicklung, Virchows Arch. f. path. Anat. **294**:365, 1935.

10. Jervis, G. A., and Kindwall, J. A.: Schilder's Disease in Ergotamine Intoxication, Am. J. Psychiat. **98**:650, 1942.

11. Collier, J., and Greenfield, J. G.: The Encephalitis Periaxialis of Schilder, Brain **47**:489, 1924.

12. Scholz, W.: Ueber Wesen, nosologische und pathogenetische Bedeutung der atypischen Abbauvorgänge bei den familiären Markerkrankungen, Monatschr. f. Psychiat. u. Neurol. **86**:111, 1933.

13. Levaditi, C.: Les ultravirus provocateurs des ectodermoses neurotropes, Ann. Inst. Pasteur **45**:673, 1930.

sion of the normal function of oligodendrocytes." Greenfield [14] again stressed the close association between demyelination and degeneration of oligodendroglia in reporting 2 cases in which these two features coexisted.

Both cases here reported showed abnormal features on the part of the glia which could be interpreted as evidence of developmental failure. Since evidence has been offered from many sides of the role of the glia in the formation and maintenance of myelin (del Río-Hortega,[15] Collier and Greenfield,[11] Scholz,[12] Greenfield [14] and Roback and Scherer [9]), it is reasonable to assume that this retarded growth and development of the glia resulted in impairment of the normal metabolism and consequent early destruction of the myelin sheaths.

SUMMARY AND CONCLUSION

The clinical and pathologic features of 2 cases of early infantile diffuse sclerosis of the brain are reported. On the basis of these and 12 other cases reported in the literature, the characteristic clinical picture of the disease is described. From a pathologic point of view, the presence of numerous immature glia elements is stressed as evidence in favor of the theory that a primary affection of the glia and consequent impairment of the normal metabolism of myelin are responsible for the pathologic process.

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14. Greenfield, J. G.: A Form of Progressive Cerebral Sclerosis in Infant Associated with Primary Degeneration of the Interfascicular Glia, J. Neurol. & Psychopath. **13**:289, 1933.

15. del Río-Hortega, P.: Tercera aportación al conocimiento morfologico e interpretación funcional de la oligodendroglia, Mem. R. Soc. españ. de hist. nat. **14**:1, 1928.

COARCTATION OF THE AORTA IN CHILDHOOD

REVIEW OF THE LITERATURE AND REPORT OF THREE CASES

PAUL H. RHODES, M.D.
AND
EDGAR DURBIN, M.D.
DENVER

In the decade between 1928 and 1938, cases of coarctation of the aorta diagnosed clinically in childhood were reported with increasing frequency. Blackford [1] in reviewing the literature for his comprehensive thesis of 1928 found only 4 cases in which the so-called "adult type" had been recognized in children during life. These cases were all reported before 1910.

While Blackford's article was in press, a case was reported by Hunter [2] and another by Hamilton and Abbott.[3] During the next ten years 30 cases [4] were reported, and 11 instances [5] have been added since

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From the Child Research Council and the University of Colorado School of Medicine and the Department of Medicine, Denver General Hospital.

1. Blackford, L. M.: Coarctation of the Aorta, Arch. Int. Med. **41**:702 (May) 1928.

2. Hunter, D.: A Case of Coarctation of the Aorta, Proc. Roy. Soc. Med. **21**: 432 (Jan.) 1928.

3. Hamilton, W. F., and Abbott, M. E.: Coarctation of the Aorta of the Adult Type: I. Complete Obliteration of the Descending Arch at Insertion of the Ductus in a Boy of Fourteen; Bicuspid Aortic Valve; Impending Rupture of the Aorta; Cerebral Death, Am. Heart J. **3**:381 (April) 1928.

4. (*a*) Poynton, F. J., and Sheldon, W. P. H.: Coarctation of the Aorta with Ulcerative Aortitis, Arch. Dis. Childhood **3**:191 (Aug.) 1928. (*b*) Thomson, A. P., and Lamb, F. W. M.: A Case of Coarctation of the Aorta, ibid. **4**:377 (Dec.) 1929. (*c*) Schlesinger, B.: Coarctation of the Aorta, Proc. Roy. Soc. Med. **23**: 119 (Dec.) 1929. (*d*) Wyllie, W. G.: Coarctation of the Aorta, ibid. **23**:829 (April) 1930. (*e*) Sheldon, W.: Two Cases of Coarctation of the Aorta, ibid. **23**:998 (May) 1930; (*f*) Coarctation of the Aorta, ibid. **24**:573 (March) 1931. (*g*) Hampson, A. C.: Coarctation of the Aorta, ibid. **25**:420 (Feb.) 1932. (*h*) Gillespie, J. B.: Coarctation of the Aorta, Am. J. Dis. Child. **43**:512 (Feb.) 1932. (*i*) Wolffe, J. B.: Coarctation of the Aorta Associated with Rheumatic Infection and Aneurysm of the Innominate Artery, Arch. Pediat. **49**:100 (Feb.) 1932. (*j*) Moncrieff, A.: Heart Disease with Abdominal Systolic Murmur: Coarctation of the Aorta, Proc. Roy. Soc. Med. **25**:720 (March) 1932. (*k*) Wilson, M. G.: Coarctation of the Aorta (Adult Type with Hypertension): Report of a Case with Diagnostic Roentgenograms, Am. J. Dis. Child. **44**:390 (Aug.) 1932. (*l*) Sheldon, W.: Coarctation of the Aorta, Proc. Roy. Soc. Med. **26**:154 (Dec.) 1932. (*m*) Amberg, S.: Diagnosis and Treatment of Coarctation of the Aorta of Adult

(Footnotes continued on next page)

1938. Thus, there have been reported in the literature at least 47 cases of coarctation of the aorta of the adult type diagnosed during life in children below the age of 15 years. With the exception of the 4 cases reported prior to 1910, these cases have been listed in the table, together with the most characteristic observations.

Type in Childhood, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 1, p. 55. (*n*) Lichtenberg, H. H., and Gallagher, H. F.: Coarctation of the Aorta: Anomaly of Great Vessels of Neck and Intermittent Leakage of a Cerebral Aneurysm Diagnosed During Life, Am. J. Dis. Child. **45**:1253 (June) 1933. (*o*) Wilkinson, K. D.: Two Cases of Coarctation of the Aorta, Proc. Roy. Soc. Med. **26**:1537 (Oct.) 1933. (*p*) Purks, W. K., and Robert, W. P.: Coarctation of the Aorta: Its Importance and Diagnosis, South. M. J. **28**:158 (Feb.) 1935. (*q*) Farris, H. A.: Coarctation of the Aorta, Canad. M. A. J. **32**:276 (March) 1935. (*r*) Vega Diaz, F.; Albert, C.; Irigoyen, A., and Suils, E.: Un caso de estenosis istmica de aorta con transposición de descendente, Arch. cardiol. y hemat. **16**:450 (Dec.) 1935. (*s*) Wile, S. A.: Coarctation of the Aorta, Am. J. Dis. Child. **51**:224 (Jan.) 1936. (*t*) Lian, C.; Abaza, A., and Frumusan, P.: Remarques cliniques sur le rétrécissement congénital de l'isthme aortique: Fréquence de la pulsatilité et de la dilatation des artères intercostales, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:782 (May 25) 1936. (*u*) Lombardi, Q.: "Doble lésion congénita." Enfermedad de Roger y estrechez del istmo de la aorta, Semana méd. **2**:1004 (Oct. 8) 1936. (*v*) Laubry, C., and Heim de Balsac, R.: Valeur des érosions costales dans le diagnostic des sténoses isthmiques, Arch. d. mal. du cœur **30**:963 (Dec.) 1937. (*w*) Rooke, E. J.: The Early Occurrence of High Blood Pressure in Coarctation of the Aorta, Brit. M. J. **1**:564 (March 12) 1938. (*x*) Eisenberg, G.: The Recognition of Coarctation of the Aorta (Adult Type) During Childhood, J. Pediat. **13**:303 (Sept.) 1938. (*y*) McNair, J. S.: Coarctation of the Aorta: Report of Case, Chinese M. J. **54**:331 (Oct.) 1938.

5. (*a*) Herkel, W.: Beobachtungen bei Aortenisthmusstenose, Ztschr. f. Kreislaufforsch. **31**:729 (Oct.) 1939. (*b*) Wilson, T. E.: A Case of Coarctation of the Aorta in Infancy, M. J. Australia **1**:589 (April 27) 1940. (*c*) Nicolson, G. H. B.: Coarctation of the Aorta in a Child with Arrested Subacute Bacterial Endarteritis and a Calcified Mycotic Aneurysm at the Seat of Stricture, Am. Heart J. **20**:357 (Sept.) 1940. (*d*) Friedman, M.; Selzer, A., and Rosenblum, H.: The Renal Blood Flow in Coarctation of the Aorta, J. Clin. Investigation **20**:107 (March) 1941. (*e*) Grishman, A.; Steinberg, M. F., and Sussman, M. L.: Contrast Roentgen Visualization of Coarctation of the Aorta, Am. Heart J. **21**:365 (March) 1941. (*f*) Eisenberg, G., and Gibson, S.: Congenital Heart Disease and the Electrocardiogram, J. Pediat. **19**:452 (Oct.) 1941. (*g*) Blumenthal, S., and Davis, D. B.: Coarctation of the Aorta in Childhood: Report of Two Cases in Which the Diagnosis Was Confirmed by the Intravenous Injection of Diodrast, Am. J. Dis. Child. **62**:1224 (Dec.) 1941. (*h*) Schwartz, S. P., and Greene, D.: Coarctation of the Aorta in Children: The Syndrome of Constriction of the Isthmus of the Aorta, with Involvement of the Origin of the Left Subclavian Artery, Am. Heart J. **23**:99 (Jan.) 1942.

An unusual form of coarctation has been reported a number of times as occurring in adults. In this type the blood pressure has been found to be high in the right arm but low in the left. Schwartz and Greene [5h] recently reported the first case of this form of coarctation in a child below the age of 15 years. In case 1 reported in this paper the condition was diagnosed in a child 9 years of age, for whom some interesting electrocardiographic tracings were obtained.

REPORT OF CASES

CASE 1.[6]—K. G., a white boy of 9 years, entered Denver General Hospital Dec. 1, 1938, with the complaints of fever and malaise for six hours. He had been apathetic for three months and had had a cough, productive of pink sputum, for two weeks. While at school the day of admission he had fallen on his left side, and afterward he had experienced pain in the left side of the chest, weakness and fever.

His mother was living and well; his father had deserted the family. He had a sister 7 years of age, living and well. A brother had died at 3 years of unknown cause.

He was a full term baby and had been bottle fed. He had lived with his paternal grandmother until her death from a pulmonary disorder three months before. He had had measles and influenza at the age of 7 years.

On examination he was poorly developed and poorly nourished and was in acute distress; his respirations were rapid and grunting. Present were circumoral pallor, reddening of the tonsils and faucial pillars and coating of the tongue. There was strong arterial pulsation in the neck. The left border of cardiac dulness was 1 cm. outside the midclavicular line; the aortic second sound was louder than the pulmonic second sound; a systolic murmur was heard at the apex, transmitted to the anterior axillary line; a systolic murmur was present at the aortic area and transmitted to the neck; the rate was rapid and the rhythm regular. Over the base of the left lung there was dulness; breath sounds were absent, and voice sounds were decreased, with rales above to the scapular spine. Over the trunk, arms and legs were numerous crusts, easily removed and leaving raised lesions with central pits.

Roentgen examination demonstrated bronchopneumonia of the left lung, maximal at the base. The transverse diameter of the heart was moderately increased because of an enlargement to the left.

Four urinalyses gave essentially normal results. The leukocyte count on entrance was 19,000, with 90 per cent polymorphonuclears. The reaction to a Kahn test was negative.

At the end of a week the temperature had dropped by lysis from 103.8 to 98.4 F. and the pulse rate from 140 to 80. Because of the persistence of the systolic murmurs and the disparity in blood pressure between the right arm (160 systolic and 102 diastolic) and the left arm (84 systolic and 44 diastolic), consultation concerning the cardiac condition was requested, and he was seen by one of us (E. D.).

The apical impulse and the left border of cardiac dulness were 6.5 cm. from the midsternal line in the fifth intercostal space. The right border of dulness was 2 cm. from the midsternum. The sounds were increased in intensity. There were a slight blowing systolic murmur and a moderate blowing diastolic murmur

6. Dr. William Wiley Jones granted permission to investigate this case.

Characteristic Findings in Coarctation of Aorta Diagnosed During Life in Childhood

Age at Diagnosis, Years	Sex	Pulsations in Neck	Pulsations in Arteries of Lower Extremities	Collateral Circulation in Region of Scapulas	Blood Pressure				Roentgenograms of Chest	Ref. No.
					Arm		Leg			
					Right	Left	Right	Left		
1 6/12	M	.....	Very weak in femoral	None visible or palpable	160/50	150/50	40/*	40/*	No erosion of ribs.....	5b
1 8/12	M	.....	None in femoral or dorsalis pedis	.....	150/110†		*	*	No erosion of ribs.....	5g
2 2/12	F	Obvious	None	None	120/90	.....	?100/*	....	.....	4f
2 5/12	F	.....	None in femoral	.....	124/86	128/100	*	*	No erosion of ribs.....	4x
3	M	.....	None in femoral	.....	140/70	145/105	*	*	No erosion of ribs.....	4x
3	M	.....	None	Present on right side	150/85	"40 mm. lower"	....	....	No erosion of ribs.....	4w
4 10/12	F	Marked	(Very feeble in right iliac)	None	150/80		....	....	.....	4o
5	F	.....	Feeble in femoral	None	175/120	200/160	125/*	125/*	.....	4b
5	M	.....	None	Present	130/100		....	....	.....	4e
5	M	On left side	None in femoral	None	140/80		105/80		.....	4u
5 6/12	F	Marked	None	None	170/		....	....	.....	4d
6	M	.....	.....	Present on left side	150/100		....	....	.....	4j
7	F	Noticeable	.....	.....	"Marked hypertension"		"Normal"		Erosion of ribs.....	4s
7	M	.....	Femoral very weak	Intercostal arteries not palpable	155/95		*	*	Pronounced erosion of ribs; defect in aortic arch	5a
7	M	.....	None in femoral	Intercostal arteries palpable	140/90	140/75	*	*	Erosion of ribs; defect in aortic arch	5d
7 6/12	F	Strong	None	.....	.....	.....	....	....	Erosion of ribs vague.....	4v
8	M	.....	.....	.....	.....	.....	....	....	.....	4a
8	M	.....	None in femoral	Present	180/120		....	....	.....	4e
8	F	Forceful	None in femoral	None	140/80	*	*	*	Erosion of ribs on right side only; defect in aortic arch	5h
9	F	Noticeable	.....	.....	220/130		120/		At 20 years, erosion of ribs; defect in aortic arch	4k
9	M	.....	None in femoral	.....	140/80	154/100	*	*	Very slight erosion of ribs at 5 years	4x

9	M	.....	.....	.....	305(?)/110	172/105	134/?	106/?	Erosion of ribs; defect in aortic arch	5d
9	M	.....	Very weak in femoral	.....	90/68	*	*	*	No erosion of ribs; defect in aortic arch	5h
10	F	.....	None in femoral	Intercostal arteries palpable	180/90		110/90		Erosion of ribs slight; coarctation visualized	5e
10	M	.....	None in femoral	Intercostal arteries not palpable	152/90	158/116	*	*	No erosion of ribs; defect in aortic arch	5f
10	M	.....	None in femoral	.....	110/70	120/90	*	*	No erosion of ribs.....	5f
11	..	Marked	Felt with difficulty	Subscapular arteries palpable	.....	.....	....	....	.....	4c
11	M	Marked	Weak on left; none on right	None	150/115	150/115	*	*	Slight erosion of ribs.....	4q
11	M	Marked	Femoral felt with difficulty	Present	154/?		90/70		Erosion of ribs.....	4y
12	M	Forceful	None	Present	150/50		....	....	Erosion of ribs.....	3
12	M	Marked	.....	Present	145/75	145/75	88/*		.....	4g
12	M	Prominent	None in femoral	Present	150/100		....	....	.....	4l
12	F	Abnormally prominent	None	Present	160/90	160/90	*	*	Erosion of ribs; defect in aortic arch	4n
12	M	.....	None in femoral or dorsalis pedis	.....	168/95	165/90	96/80	98/84	No erosion of ribs; coarctation visualized	5e,g
12 6/12	M	Marked	None in femoral	.....	170/100		....	....	Erosion of ribs; defect in aortic arch	4v
13	M	.....	Femoral +2 on basis of +4	Intercostal arteries palpable	"Above normal"		....	....	.....	4h
13	F	Marked	None	.....	206/148	145/100	*	*	Erosion of ribs (bilateral); defect in aortic arch	4l
13	M	.....	Doubtful	Present	170/90	170/90	110/78		No erosion of ribs.....	4m
13	M	Extensive	.....	Present	210/110	220/120	125/80	125/95	Erosion of ribs; coarctation demonstrated	4r
13	M	.....	.....	None	170/90		130/60		No erosion of ribs.....	4t
14	M	Heaving	None	Present	165/90	155/85	....	....	.....	2
14	M	.....	None	Present	198/135		....	....	.....	4o
14	M	Marked	Femoral feeble; none in popliteal or dorsalis pedis	None	195/80	180/70	*	*	Pronounced erosion of ribs..	4p

* Not obtainable.

† Centered figures indicate that the side was not stated.

continuous with the second sound at the apex. At the pulmonic area, and louder at the aortic area, was a systolic murmur; this was heard on both sides of the neck, more distinctly on the right. There was a very slight systolic murmur as well as easily heard cardiac sounds in the left side of the chest posteriorly. A strong pulsation was noted in the suprasternal notch, synchronous with the carotid pulsations. The blood pressure in the right arm was 182 systolic and 94 diastolic and in the left arm 84 systolic and 60 diastolic; in the right leg 96 systolic and 68 diastolic, and in the left leg 102 systolic and 86 diastolic. A diagnosis of adult type coarctation of the aorta was made.

An electrocardiogram showed a sinus rhythm, with a rate of 75, a QS interval of 0.09 second with a high voltage and a tendency to right axis deviation ($QRS_1 = +6 - 7$ mm., with 1 millivolt = 5 mm.). The T waves in leads I and III were flat. The P waves in leads I and II were broad.

On restudy of the roentgenograms it was noted there was a perceptible irregularity of the inferior borders of the third to eighth ribs on the right. There was also an "inner shadow" of the supracardiac vessels at the level of the sixth intercostal space posteriorly. A right lateral picture showed that the anterior mediastinum was encroached on; the aortic shadow ended at the level of the seventh dorsal vertebra.

On December 19 he was discharged to his mother and directed to return to the cardiac disease clinic. However, he was not seen further until he was sent to the Child Research Council from a local orphanage as a supposedly normal subject for a test of cardiovascular function.

On Jan. 20, 1940, he was a subject in the prolonged standing test; in addition, simultaneous recordings of lead III on the electrocardiograph were taken. A tilt-top table was used. Determinations of blood pressure were taken on the right arm at one or two minute intervals, a mercury manometer and a 9 cm. cuff being used. Pronounced hypertension was found, with systolic pressure 160 mm. and diastolic 98 mm. After twenty minutes' rest the readings had dropped to 150 systolic and 92 diastolic. As the electrocardiograph electrodes were already connected, the blood pressure was not taken on the left arm at this time, and it was decided to continue with the test.

The child was tilted from the horizontal to the vertical position; five minutes later the blood pressure had dropped to 136 systolic and 72 diastolic. Shortly afterward he became pale, slumped and appeared on the verge of fainting. His knees did not give way, and he was kept from swaying to the side until the table could be lowered to the horizontal position, which was done after nine and one-half minutes in the vertical position. The child appeared semiconscious and remained so for several minutes; in about five minutes his color returned and he appeared alert; after several more minutes he fell asleep.

After the horizontal position was regained, the blood pressure gradually rose to 150 systolic and 86 diastolic in five minutes and leveled off at 162 systolic and 90 diastolic after ten minutes. Coarctation of the aorta was suspected, and after the electrocardiographic tracing was completed the blood pressure was taken on the left arm. To our surprise the reading was 90 systolic and 74 diastolic. Determinations made on the legs, with the 9 cm. cuff just above the knee and the stethoscope bell on the popliteal space, gave the following readings: right leg, 100 systolic and 76 diastolic; left leg, 110 systolic and 80 diastolic. At a later date determinations from the arms showed: right, 154 systolic and 104 diastolic; left, 98 systolic and 82 diastolic. This striking difference between the two arms

is graphically depicted in figure 1. Readings taken from the legs, with a 13 cm. cuff and with the leg supported between two tables so that the cuff was free, gave the following results: right leg, 92 systolic and 70 diastolic; left leg, 94 systolic and 72 diastolic. The electrocardiographic tracing is discussed later.

Physical Examination (Jan. 25, 1940).—The patient was a small, slender, rather poorly developed and only fairly well nourished boy of 10 years. He was quiet and shy but cooperative. His height was 133 cm. (4 feet 4½ inches) and his weight 27.7 Kg. (61 pounds).

Skin: His skin was clear, and there was no cyanosis.

Vessels: Forceful arterial pulsations were visible in the suprasternal notch, on both sides of the neck along the course of the carotid arteries, above the medial two thirds of the right clavicle, below the lateral third of the right clavicle and in the right axilla. Pulsation could be neither seen nor felt above the left

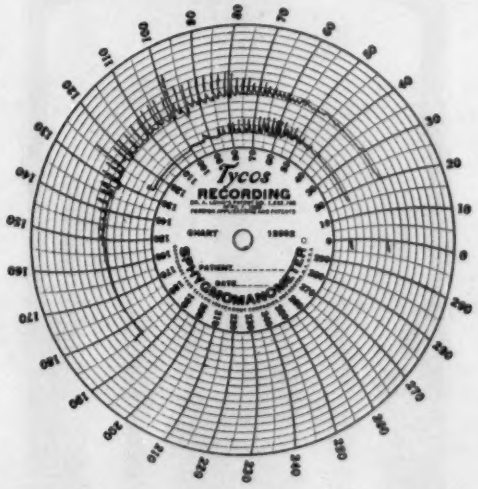

Fig. 1.—Striking difference in blood pressure readings between the arms. The outer tracing is from the right arm; the inner tracing, from the left arm.

clavicle or in the left axilla. A small pulsating vessel, 2 to 3 mm. in diameter, crossed the left clavicle near the manubrium. Posteriorly, two small pulsating areas were seen in the right interscapular area, one just below the level of the spine and the other near the inferior angle of the right scapula. On closer inspection the faint outline of a small vessel was seen running diagonally across the right scapula from the region of the right posterior axillary line to the lower pulsating area; pulsation could be felt but not seen in this vessel. This collateral circulation is shown in figure 2. No arteries were seen or felt on the left side of the back.

The right radial pulse was full and bounding; in contrast, the left radial pulse was small and weak. The left brachial pulse was palpable but much weaker than that on the right. Pulsations were felt with some difficulty in the abdominal aorta. Reduced but easily palpable pulsations were present in the femoral arteries in the region of the inguinal ligament. The popliteal arteries were fairly readily felt. The left dorsalis pedis artery was readily palpated; the right, with difficulty.

On simultaneous palpation of the right radial and right femoral pulses, the femoral was perceptibly later than the radial.

Chest: The region along the right costochondral junction was more prominent than that on the left side.

Heart (standing): The apex impulse was forceful and diffuse, maximal 7.5 cm. to the left of the midsternal line in the fifth intercostal space. The left border of dulness was 7.5 cm. from the midsternal line (in the sixth intercostal space); the right border of dulness, 3.0 cm. from the line (in the fourth intercostal space).

Fig. 2.—K. G., aged 10 years. The posterior view shows the location of the collateral circulation in the region of the right scapula.

The rhythm was regular; the rate, 80. The aortic and pulmonic second sounds were both loud and about equal in intensity. A blowing systolic murmur was heard over the aortic area and transmitted up the neck vessels, more loudly on the right than on the left. A softer, less intense systolic murmur was heard along the left border of the sternum in the second and third intercostal spaces. A moderately loud systolic murmur was heard along the entire right border of the sternum down to the costal margin. Over the apex was heard a short systolic murmur and a slightly longer diastolic murmur. A faint systolic murmur was heard in the interscapular area. No murmur was heard over the pulsating vessels. No thrills were palpated.

Eyes: The eyes were normal except on ophthalmoscopic examination, in which the retinal arteries appeared narrow and more tortuous than normal although no pulsation was seen. The veins were not unusual, and the disks were normal.

Extremities: There was no clubbing of the fingers or toes. The left arm from the shoulder to the tips of the fingers was approximately 1 cm. shorter than the right arm. The circumference at the middle of the upper part of the left arm was 1 cm. less than that of the right arm; there was less difference in the forearms.

The remainder of the physical examination revealed no unusual conditions. A tonsillectomy was done on July 26, 1940, with an uneventful convalescence.

Later Examinations (Aug. 29, 1940).—The prolonged standing test was repeated in an attempt to obtain the abnormal rhythm on lead II of the electrocardiogram. After standing for several minutes the child complained of nausea and precordial pain. At that time a short record was obtained which showed a change from normal rhythm to one resembling nodal rhythm (?) (fig. 9). While standing, the blood pressure dropped to 130 systolic and 70 diastolic in the right arm. When the boy was returned to the lying position he fell asleep almost at once. The blood pressure went up to 186 systolic and 100 diastolic; then it gradually fell over a period of thirty minutes to approximately the original reading, of 164 systolic and 96 diastolic.

(Feb. 4, 1941).—His height was 138 cm. (4 feet 6⅓ inches) and his weight 29.8 Kg. (65½ pounds). The blood pressure in the supine position, measured with a 9 cm. cuff, was 166 systolic and 114 diastolic in the right arm and 102 systolic and 76 diastolic in the left arm. In the right hypochondrium a dilated pulsating artery appearing like a cirsoid aneurysm was noted.

(Feb. 10, 1942).—His height was 141.7 cm. (4 feet 7¾ inches), and his weight 32.5 Kg. (71½ pounds). Blood pressure in the supine position was 148 systolic and 92 diastolic in the right arm and 94 systolic and 72 diastolic in the left arm with the 9 cm. cuff, and 142 systolic and 90 diastolic and 92 systolic and 68 diastolic with the 13 cm. cuff. The systolic murmur at the apex seemed increased in duration and intensity. No other changes were noted in the physical examination.

Roentgenologic Examination.—The posteroanterior film (fig. 3) revealed pronounced hypertrophy of the left ventricle, as shown by the thick, rounded apex extending well beyond the midclavicular line. There was slight enlargement of the right ventricle, seen best in the oblique film (not illustrated). The ascending aorta was not appreciably dilated. The shadow of an aortic knob was not demonstrated. There was some increased prominence of the pulmonary artery region. The posteroanterior roentgenogram also revealed a rounded shadow inside the upper left cardiac border; this shadow may represent dilatation of the descending aorta just below the stricture. Slight but definite erosion of the lower posterior border of the third, fourth, and fifth ribs on the right side was shown (figs. 3 and 4). There was some roughness of the sixth, seventh and eighth ribs on the right side. The erosion was best observed by comparing the right and the left ribs, as no erosion was present on the left side. The film taken midway between the left posteroanterior oblique and lateral positions fails to demonstrate the aortic arch at the beginning of the descending limb (fig. 5).

The roentgenograms did not show a cervical rib.

Electrocardiographic Observations.—The continuous tracing of lead III, taken during the prolonged standing test, will be described first. The voltage was reduced

as far as possible in order to bring a huge R wave completely on the film (1 millivolt = 3.5 mm.). The record in the initial recumbent position was not remarkable (fig. 6*A*); the T waves were slightly diphasic. The heart rate was 68 per minute.

During eight minutes of standing, the electrocardiogram was recorded for five periods totaling two minutes. In this time there was a slight sinus arrhythmia, the rate varying from 68 to 95 per minute, most of the time between 75 and 88 per minute. The amplitude of the P wave varied from zero to plus 1 mm. The amplitude of the QRS complex varied slightly, from $-1.5+14.5$ mm. to $-2+16$ mm. The T wave varied from $+1$ to $-1+1$. The PR interval was

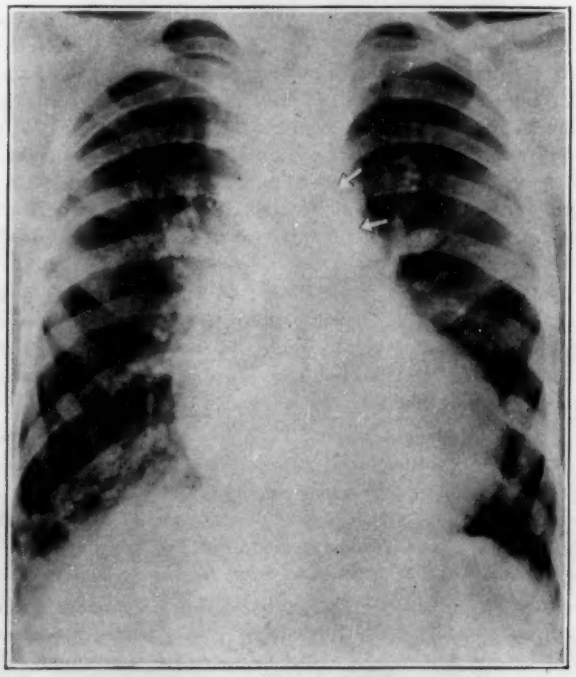

Fig. 3.—Posteroanterior roentgenogram of the chest, showing hypertrophy of the left ventricle and slight erosion of the lower posterior border of the right third, fourth and fifth ribs. No erosions of the ribs are seen on the left side. The curved shadow inside the cardiac border, between the two arrows, may be the outline of the dilated descending aorta just below the stricture.

fairly constant, changing from 0.14 to 0.16 second. The QS interval, likewise, was constant, measuring 0.09 or 0.10 second (fig. 6, *B* and *C*).

Shortly after this a similar period of normal complexes, fourteen in number, with the RR intervals varying from 0.84 to 1.03 second (rate 71 to 58 per minute) was recorded. The next RR interval was 1.06 second and was followed by two "transitional" M form QRS complexes, and then a definitely aberrant complex, measuring $+3.5-7$ mm., with a width of 0.14 second (fig. 6*D*). This complex was preceded by a barely perceptible P wave, and the PR interval was 0.04 second. The T wave following measured $+4.5$ mm. Then came two M form

QRS complexes and then four aberrant complexes, three normal complexes, one M form complex, seventeen aberrant complexes (fig. 6 *E*), five normal complexes, two M form complexes and eight aberrant complexes.

After this, the patient was lowered to the supine position, and for two and one-half minutes aberrant QRS complexes recurred (fig. 6, *F* and *G*) in thirteen groups of varying length, the longest nine in number.

Throughout the record the normal complexes occurred in sinus arrhythmia until such time as the RR interval became more prolonged, and then they were

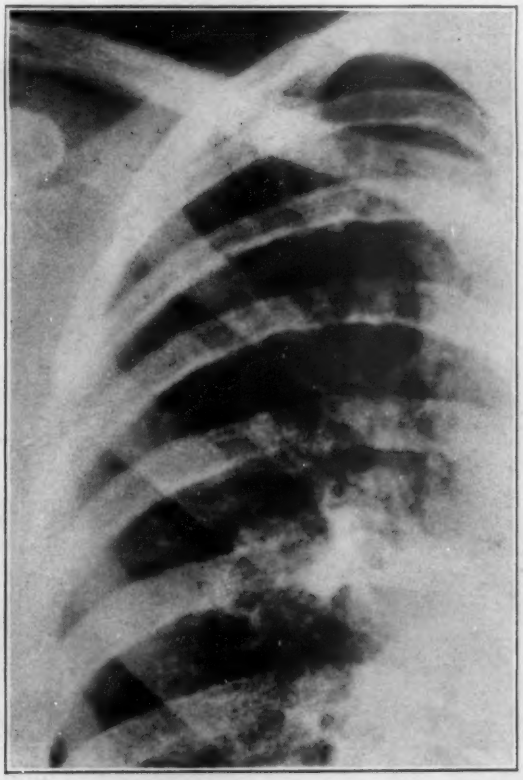

Fig. 4.—Enlarged view of the right side of the thorax, showing slight erosions of the ribs, most evident on the third, fourth and fifth.

replaced by "transitional" complexes and aberrant complexes. Each time the normal complexes recurred, it was after an RR interval shorter than that between aberrant complexes.

The RR interval between aberrant complexes was remarkably constant, at first being 0.98 second and the interval at the end of the record 1.10 second. The RR interval between normal complexes at the beginning varied between 0.84 and 1.03 second, and at the end between 0.83 and 1.24 second.

The QS interval of normal complexes was 0.08 to 0.10 second, that of "transitional" complexes 0.08 to 0.14 second and that of aberrant complexes 0.11 to 0.16 second.

P waves could not be seen preceding the aberrant complexes except before the first one, when the PR interval was 0.04 second. The PR interval before "transitional" complexes varied from 0.08 to 0.15 second, usually being 0.12 second. The normal PR interval was 0.12 to 0.16 second, usually 0.12 second.

From the measurements just noted, it was concluded that when the sinus arrhythmia became too pronounced lower centers took the pacemaking function away from the sinus node and produced a regular rhythm. In many cases of sinus depression the period of depression is relatively short and there is a cardiac standstill of short duration, the sinus node regaining its activity before the junctional tissue or ventricular foci can give rise to an arrhythmia. Sometimes with

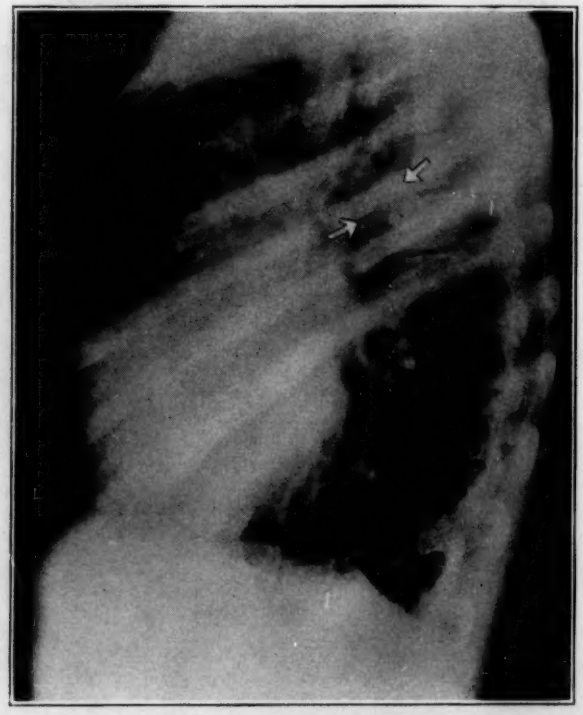

Fig. 5.—Roentgenogram of the chest taken midway between the left posteroanterior oblique and the lateral position to show the break in continuity of the aortic arch. The arrows point to the borders of the aorta below the coarctation. Proximal to the arrows the outline of the aorta disappears.

this sinus arrest, a ventricular escaped beat occurs. In this patient, however, the pronounced sinus arrhythmia resulted in a longer interval than usual, and lower centers, with an intrinsically faster rate than that of the sinus node at the time of the arrest, took over the rhythm at once. This was maintained until the sinus node regained its activity and could take over the pacemaking function again.

An ordinary electrocardiogram was then taken and repeated at a later date (fig. 7 *A*). These showed huge voltages for the QRS complexes and right axis

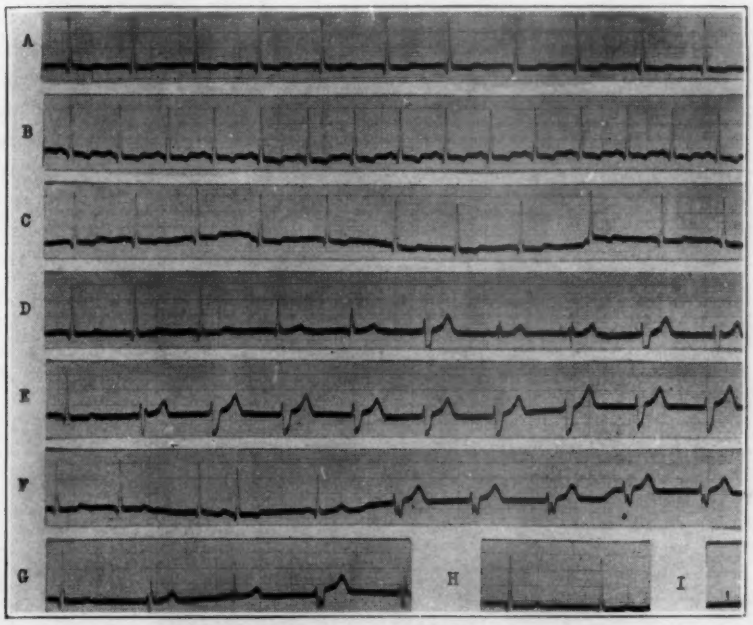

Fig. 6.—Sections from a continuous tracing of lead III taken during the prolonged standing test. Voltage reduced, 0.35 cm. deflection corresponding to 1 millivolt. *A*, initial recumbent position. *B*, after six minutes in standing position. *C*, after seven minutes in standing position. *D*, appearance of abnormal ventricular complexes after eight and one half minutes in standing position. *E*, second group of abnormal complexes, separated from first group by three "normal" complexes. *F*, reappearance of abnormal complexes thirty seconds after return to recumbent position. *G*, last group of abnormal complexes, recorded two minutes later. *H*, normal complexes, present one minute after *G*. *I*, standardization.

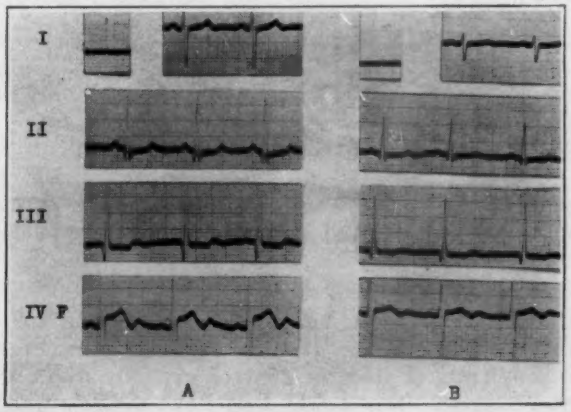

Fig. 7.—Electrocardiograms showing the three standard leads and lead IV F, taken after recovery from the prolonged standing test. *A*, taken with the usual voltage, 1 cm. deflection equivalent to 1 millivolt. *B*, taken with reduced voltage, 0.35 cm. equivalent to 1 millivolt.

deviation. In order to bring the R waves in leads II and III entirely on the film, the voltage was reduced as far as possible (fig. 7 *B*). From the amplitudes at the reduced voltage it was estimated that with the usual voltage (1 cm. deflection corresponding to 1 millivolt of potential) these waves would be 31 and 46 mm., respectively. In addition to the diphasic T wave in lead III, previously mentioned,

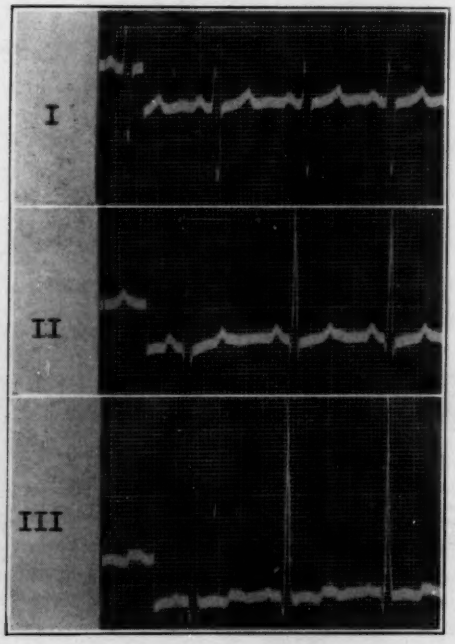

Fig. 8.—Electrocardiogram taken with string galvanometer to show amplitude of the deflections (R waves retouched in leads II and III). $R_2 = 28.5$ mm.; $R_3 = 43.0$ mm.

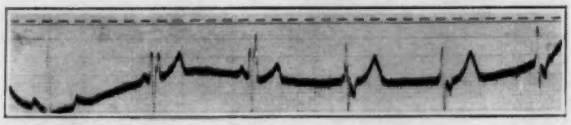

Fig. 9.—A short period of abnormal rhythm recorded on lead II during a repeat prolonged standing test done seven months after the initial test. One millivolt = 1.0 cm.

the T wave in lead IV was also diphasic. The ST segment was depressed in leads II and III and elevated in lead IV. The PR (PQ) interval was 0.16 second.

When the patient was 12 years old a record was taken with a string galvanometer electrocardiograph. This showed a right axis deviation with normal conduction time (PR = 0.16 second, QS = 0.10 second) and high amplitude of the QRS complexes in all leads (fig. 8).

On Aug. 29, 1940 the standing test was repeated, and a short strip of lead II (reproduced in fig. 9) showed that a normal QRS complex was followed at an

increased interval by two wider, M form complexes and that these, in turn, were followed by three still wider, aberrant complexes, which were not preceded by P waves. Whereas in the initial record of lead III the P waves preceding the normal complexes were low in amplitude and rather difficult to identify, here in lead II the P waves preceding the normal QRS complex and the two "transitional" complexes were easily seen. Hence, failure to detect them previously or here in the last three aberrant complexes denotes a true absence and strengthens the belief that they were absent also in the earlier record (lead III) and not hidden in the aberrant QRS complexes.

CASE 2.—C. S., a white girl of 11 months, was brought to Denver General Hospital Dec. 31, 1937, because of cough and hoarseness of two weeks' duration and a temperature of 103 F.

Her father was 22 years old and her mother 19; both were living and well. One brother, 2 years of age, was living and well.

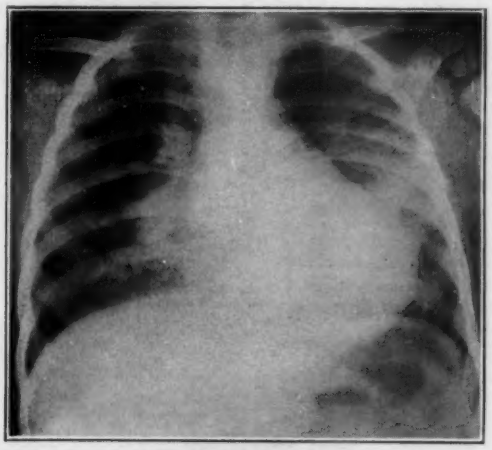

Fig. 10.—C. S. Posteroanterior roentgenogram of the chest taken at 11 months.

She was a full term baby, breast fed for three months, and her development was normal.

On examination she appeared undernourished (weight 15 pounds 14¾ ounces [7,222 Gm.]) and coughed paroxysmally. Her respiration was grunting. Other evidences of bronchopneumonia were present. At this time the heart was normal on ordinary examinations.

A restudy of the roentgenogram taken then revealed enlargement to the left, with a blunt, rounded apex (fig. 10). No electrocardiogram was taken.

Her recovery from pneumonia was complicated by bilateral mastoiditis with mastoidectomy, and then by measles; she was not discharged from the hospital until April 3, 1938.

On May 18, 1941, when 4 years old, she was brought in again with the story of having fainted and having had clonic clenching of the jaws while unconscious. She had vomited and was feverish.

Bronchopneumonia was diagnosed. Because of a loud blowing systolic murmur over the entire precordium, maximal over the pulmonic area and transmitted to the axilla and back, it was felt there was a congenital cardiac lesion.

Recovery under sulfanilamide medication was prompt, and she was discharged on May 24.

Seen in the cardiac clinic June 9 (by E. D.), she seemed well. The left border of cardiac dulness was 5.5 cm. from the midsternum; the right border, 2 cm. The heart sounds were normal. A slight thrill was felt in the third left intercostal space 3 cm. from the midsternum, and a moderate systolic murmur of low pitch was heard maximally in this location. The murmur was heard slightly in the neck and medial to the left scapula. In the right arm the blood pressure was 144 systolic and 104 diastolic; in the left, 128 systolic and 80 diastolic; in the legs it was not obtainable. Pulsations could not be felt in the left femoral or left posterior tibial arteries.

Review of the roentgenogram taken during hospitalization showed a heart increased in length. An electrocardiogram showed left axis deviation, sinus

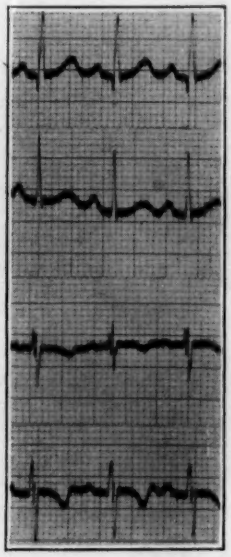

Fig. 11.—C. S. Electrocardiogram taken at 4 years.

tachycardia (rate 125) and inverted T waves in leads III and IV F (fig. 11). A diagnosis of coarctation of the aorta of the adult type was made.

On July 14, a systolic murmur was heard at the base of the heart and over the carotid arteries. There was a slight pulsation in the suprasternal notch but none in the back, in the abdominal aorta, in the femoral or in the posterior tibial arteries. The blood pressure taken simultaneously in both arms was 128 systolic and 84 diastolic; it could not be obtained in the legs by auscultation or by oscillation of the mercury column.

At the age of 5 years she was again brought to the hospital with pneumonia and responded well to sulfathiazole, being discharged after two weeks. During her stay her blood pressure was recorded as high as 150 systolic and 96 diastolic. Repeated urinalyses showed normal urine.

The apical impulse and the left border of cardiac dulness were 6 cm. from the midsternal line in the fifth intercostal space; the right border, 2 cm. from the

line in the fourth space. The apical sounds were normal, the pulmonic second sound normal and louder than the aortic second sound. There was a slight systolic murmur at the cardiac apex, along the left sternal border and at the base of the heart. A slight systolic murmur was heard over the entire back of the chest, but heard best in the interscapular area. A systolic murmur was heard over the carotid arteries. With the patient in the supine position, the precordial systolic murmur was maximal along both sternal borders. No systolic murmur could be heard in the abdomen. Bilateral carotid pulsations were the only abnormal pulsations. Femoral pulsations could not be definitely felt. The abdominal aorta was not felt.

Blood pressure, taken simultaneously by two observers, was 134 systolic and 76 to 60 diastolic in the right arm and 124 systolic and 76 to 68 diastolic in the

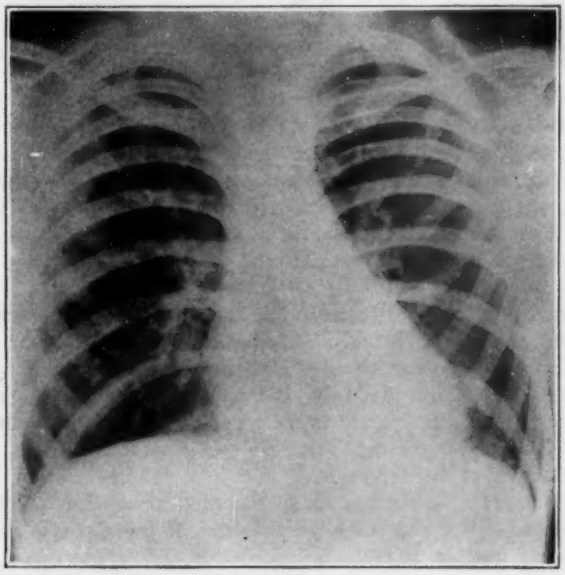

Fig. 12.—Posteroanterior roentgenogram of the chest of C. S. taken at 5 years.

left arm. When the observers changed sides, it was 134 systolic and 76 to 60 diastolic in the right arm and 125 systolic and 80 to 68 diastolic in the left arm. In the legs oscillations occurred from 84 to 50, but sounds could not be heard.

Oscillometric study by Drs. Gerald H. Smith and R. W. Moody, using the Boulitte machine and a 6 cm. band, gave maximal deflections (2 degrees) from 120 to 80 in the right arm and from 110 to 80 in the left arm. In the left leg oscillations of 1.5 degrees occurred from 90 to 70; in the right leg oscillations of 1.25 degrees occurred from 100 to 80.

Roentgen study showed slight enlargement of the left ventricle; the aortic knob was not visualized. Notching of the ribs was not present (fig. 12).

When last seen in the cardiac disease clinic, April 20, 1942, she appeared well. The blood pressure was 124 systolic and 60 diastolic in the right arm and 116 systolic and 58 to 50 diastolic in the left arm. The systolic murmur was unchanged.

CASE 3.—G. M., a white boy of 4 years 4 months, was referred to us by Dr. John M. Nelson, who had found hypertension present in the arms with low pressure in the legs and had made the diagnosis of coarctation of the aorta. The past history was uneventful except for repeated sore throats. A tonsillectomy was done at the age of 3 years without complications.

Examination revealed a well developed and well nourished boy, a little apprehensive but cooperative. His cheeks appeared slightly flushed. Only slight arterial pulsations were visible in the neck. No abnormal pulsations were found on the back or elsewhere. The radial pulses were full and equal. Pulsations were not felt in the abdominal aorta. Pulsations were not definitely felt in either femoral, popliteal or posterior tibial artery. There were questionable pulsations in the dorsalis pedis arteries.

Heart: With the patient standing, a slight systolic thrill was felt at the apex. The apical impulse was 5.5 cm. from the midsternal line in the fourth intercostal space, the left border of dulness 5.5 cm. from the line in the fourth and fifth spaces and the right border 2.5 cm. from the line in the fourth space. The apical sounds were clear; the pulmonic second sound was of normal intensity and greater than the aortic second sound, which was reduced. A slight blowing systolic murmur of medium pitch was heard at the apex, along the left sternal border and over the base of the heart. There was a moderate systolic murmur, rough in character, over both carotid arteries and under both clavicles. A slight systolic murmur of low pitch was heard in the left axilla, over the upper posterior part of the chest and in the interscapular area down to the angles of the scapulas. With the patient in the supine position, the precordial systolic murmur was of moderate intensity along the left sternal border.

Blood pressure taken with the patient in the standing position with the 9 cm. cuff was 144 systolic and 78 to 70 diastolic in the right arm and 138 systolic and 76 to 66 diastolic in the left arm. When the supine position was assumed, the reading for the left arm was 143 systolic and 76 to 68 diastolic. In the legs, with the 13 cm. cuff and the patient in the prone position, faint sounds were heard from 102 to 88 mm. over the right leg. No sounds were heard over the left leg, but slight oscillations of the mercury were seen from 94 to 54 mm.

The posteroanterior roentgenogram of the chest revealed no cardiac enlargement, and erosion of the ribs could not be seen. It was felt that the film taken midway between the left posteroanterior oblique and lateral positions gave no positive evidence either for or against coarctation.

The electrocardiogram showed no axis deviation. The R wave in lead II had an amplitude of 22 mm.

Urinalysis revealed entirely normal conditions.

The diagnosis of coarctation of the aorta of the adult type was confirmed.

COMMENT

Pathogenesis.—The pathogenesis of coarctation of the aorta in childhood was reviewed recently by Blumenthal and Davis.[5g] Blackford,[1] Evans [7] and other recent writers agree that Bonnet's [8] "adult" type, as well as his "infantile" type, is due to maldevelopment occurring in early embryonic life, in the region where the left dorsal aorta is joined by the

7. Evans, W.: Congenital Stenosis (Coarctation), Atresia, and Interruption of the Aortic Arch, Quart. J. Med. **2**:1 (Jan.) 1933.

8. Bonnet, cited by Blackford.[1]

left fourth and left sixth (ductus arteriosus) aortic arches. The fundamental difference in classification appears to involve the location of the constriction in relation to the ductus arteriosus. Ballantyne [9] suggested that if the defect in the aorta obstructed the flow of the blood from the ductus a collateral circulation would develop in early fetal life, enabling the person to survive beyond infancy. Blumenthal and Davis,[5g] believing that the terms adult and infantile are misnomers, have suggested "compensating coarctation" for the former and "noncompensating coarctation" for the latter.

Diagnosis.—The diagnosis of the adult or "compensating" type was fully covered by Abbott [10] in her exhaustive article. Blumenthal and Davis [5g] recently discussed the diagnosis with regard to childhood. We wish to consider this in more detail after reviewing 43 cases in which the condition was diagnosed during life in children. The youngest patient in whom the condition was recognized during life was a boy 18 months of age. The diagnosis was made by Dr. T. E. Wilson.[5b]

Pulsations: Case reports frequently mention the presence of forceful pulsations visible in the suprasternal notch and along the course of the subclavian and carotid arteries. Such pulsations should first arouse the suspicion of obstruction in the aorta.

Eisenberg [4x] expressed the belief that palpation for pulsations in the femoral arteries is the simplest and most direct method of making the diagnosis. This is supported by the fact that in 34 cases in which this examination was noted femoral pulsations were not found in 24 cases and only feeble pulsations in 10.

Besides being weak, the femoral pulse is also retarded in coarctation of the aorta. Normally the femoral pulse precedes the radial pulse by 0.01 to 0.02 second. In coarctation the femoral pulse lags behind the radial pulse; this point was emphasized by Abbott [10] and by Railsback and Dock.[11] As Lewis [12] pointed out, the delay in starting of the femoral pulse is probably not detectable clinically (0.03 second average in 6 cases studied by him). The palpable delay should be attributed to the slowness with which the femoral pulse rises to and attains its summit (0.145 second average lag behind the radial).

In several cases in children the retinal arteries have been described as constricted and tortuous. In the case reported by Lichtenberg and

9. Ballantyne, E. N.: Coarctation of the Aorta: Report of Three Cases, Am. J. Dis. Child. **50**:642 (Sept.) 1935.

10. Hamilton and Abbott.[3] Abbott, M. E.: Coarctation of the Aorta of the Adult Type: II. A Statistical Study and Historical Retrospect of Two Hundred Recorded Cases, with Autopsy, of Stenosis or Obliteration of the Descending Arch in Subjects Above the Age of Two Years, Am. Heart J. **3**:574 (June) 1928.

11. Railsback, O. C., and Dock, W.: Erosion of the Ribs Due to Stenosis of the Isthmus (Coarctation) of the Aorta, Radiology **12**:58 (Jan.) 1929.

12. Lewis, T.: Material Relating to Coarctation of the Aorta of the Adult Type, Heart **16**:205 (June) 1933.

Gallagher [4n] and in the one reported by Nicolson,[5c] it was noted that the retinal vessels were also pulsating.

Collateral Circulation: The statement by recent authors that a superficial collateral circulation is rarely found over the back in children is not confirmed by a review of the reported cases in children. Of 29 cases in which this detail was noted, visible or palpable vessels were present in the region of the scapulas in 17 and absent in 12. In the remaining 14 cases no statement was made that this part of the examination was done. The youngest child in whom a collateral circulation was found was 3 years old.[4w] It is probable that it would be found more often if it were searched for carefully. The superficial arteries most frequently seen are branches of the subclavian and axillary arteries, especially the scapular circumflex (dorsal scapular) branch of the subscapular artery, passing across the back to anastomose with branches of the aortic intercostal arteries. The superior intercostal arteries anastomosing with the aortic intercostal arteries and the internal mammary arteries anastomosing with the epigastric arteries below form an important and often the principal collateral pathway but are seldom visible or palpable. Dilated epigastric arteries resembling cirsoid aneurysms are sometimes seen on the abdomen.

Blood Pressure: King [13] in 1937 reviewed 175 cases of coarctation, including 5 of his own, in which determinations of blood pressure were available. In coarctation the pressure in the arms is higher than in the legs; this is the reverse of the normal condition.

In cases of coarctation there are usually slight differences in the pressure in the arms. However, occasionally a case is encountered in which the pressure is high in the right arm and low or normal in the left arm. Autopsy in some of these cases has shown the coarctation to be present at the origin of the left subclavian artery or between the left carotid and the left subclavian artery. The mouth of the left subclavian artery may be narrowed, or there may be a congenital atresia of the proximal part of the artery. In Rooke's [4w] case there are certain features which suggest this atypical type of coarctation. The blood pressure was "always about 40 mm. lower" in the left arm, and pulsations were found only on the right side of the back. However, the radial pulses were reported to be full. Schwartz and Greene [5h] were the first to report a definite case of this type of coarctation in a child. These authors have reviewed and discussed this type.

Love and Holms [14] have reported a unique case of coarctation in an adult with the blood pressure considerably higher in the left arm than in the right. At autopsy the right subclavian artery was found to be

13. King, J. T., Jr.: The Blood Pressure in Stenosis at the Isthmus (Coarctation) of the Aorta: Case Reports, Ann. Int. Med. **10**:1802 (June) 1937.

14. Love, W. S., Jr., and Holms, J. H.: Coarctation of the Aorta with Associated Stenosis of the Right Subclavian Artery, Am. Heart J. **17**:628 (May) 1939.

extremely narrow at its origin from the innominate artery. East [15] presented a clinical case with the blood pressure higher in the left arm.

Roentgenography: The roentgenographic diagnosis of coarctation has been presented ably by Fray.[16] He considered the most reliable single condition to be the defect in the aortic arch seen in the left posteroanterior oblique film.[17] In adults with coarctation the aortic knob is absent in the posteroanterior view; however, as noted by Fray, this aortic shadow in early life is normally absent or inconspicuous; hence this sign is not reliable in youth.

Hypertrophy of the left ventricle, dilatation of the ascending aorta and erosion of the lower margin of the ribs are indirect signs. Although erosions of ribs are visible in the roentgenogram of Hamilton and Abbott's patient,[3] Rösler [18] was the first to describe this condition in roentgenograms. He demonstrated also the absence of the aortic knob and the break in the aortic arch in adults. Railsback and Dock [11] and Ernstene and Robins [19] pointed out the presence of erosion of ribs in roentgenograms; the latter authors took roentgenograms of the chest of an adult after postmortem injection of the arterial vascular system with a contrast medium and demonstrated both the site of the coarctation and the extreme tortuosity and dilatation of the intercosal arteries. It evidently requires a period of years for erosion of ribs to develop. Eisenberg [4x] reported the case of a 5 year old child showing very slight erosion of the ribs. Erosion if present is considered pathognomonic of coarctation, but its absence does not rule out the condition.

Lian, Marchal and Abaza [20] described a "double aortic knob" in the posteroanterior roentgenogram of 1 of their patients. This appeared

15. East, T.: Coarctation of the Aorta, Proc. Roy. Soc. Med. **25**:796 (April) 1932.

16. Fray, W. W.: The Roentgenologic Diagnosis of Coarctation of the Aorta (Adult Type), Am. J. Roentgenol. **24**:349 (Oct.) 1930.

17. Fray believed that the aortic arch could be shown in the left oblique position even in infants and in young children. At the Child Research Council for the past year oblique views have been taken routinely for our series of normal children. In many of the younger children it has been difficult to outline the aortic arch. Consequently, when an attempt is made to demonstrate a defect in the arch, the age of the child should be taken into consideration. We have found that the arch often can be seen best in a film taken midway between the left posteroanterior oblique and lateral positions.

18. Rösler, H.: Beiträge zur Lehre von den angeborenen Herzfehlern; Untersuchungen an zwei Fällen von Isthmusstenose der Aorta, Wien. Arch. f. inn. Med. **15**:521 (July) 1928.

19. Ernstene, A. C., and Robins, S. A.: The Roentgenologic Diagnosis of Stenosis of the Descending Arch (Coarctation) of the Aorta, Am. J. Roentgenol. **25**:243 (Feb.) 1931.

20. Lian, C.; Marchal, M., and Abaza, A.: Le diagnostic radiologique, du rétrécissement congénital de l'isthme de l'aorte, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:773 (May 25) 1936.

as a smaller arc inside the usual arc of the aortic knob. They believed that this second, smaller, arc corresponded to the descending aorta below the stricture. This inner arc may be similar to the rounded shadow inside the upper left cardiac border shown in the posteroanterior film of our case 1 (fig. 3).

Robb and Steinberg,[21] using their diodrast method, visualized the site of coarctation in Nicolson's case.[5e] Visualization with a contrast medium was also used to localize the coarctation in the case reported both by Grishman, Steinberg and Sussman [5e] and by Blumenthal and Davis.[5g] This procedure will no doubt be used in the future to aid in the diagnosis of coarctation accompanied by indefinite clinical signs or by other cardiovascular anomalies.

The Electrocardiogram: The importance of the electrocardiogram in the diagnosis of coarctation has been a controversial subject. Abbott [10] said it "almost invariably" showed a left-sided preponderance. Lewis [12] and Wolke [22] said it "usually" showed a left-sided preponderance. On the other hand, it has been stated by others (King,[23] Eisenberg,[24] Appelbaum and Kalkstein [25]) that the electrocardiogram is of no value in diagnosis. Master [26] pointed out that a left axis deviation is often observed, but added that in several cases of coarctation known to him this feature was not shown. Graybiel and White [27] stated that the electrocardiogram may be normal in occasional instances of coarctation. Schnitker [28] evaluated the electrocardiographic results on the basis of the degree of coarctation and of the coexistent cardiac defects: If the constriction is moderate or pronounced and otherwise uncomplicated, a left axis deviation is found; if there is a strain on the right side of the heart, as from a widely patent ductus arteriosus or a large interauricular septal defect, right axis deviation may occur.

The authors have found in the literature (exclusive of that covered by Abbott [10] in 1928) 116 cases (involving patients of all ages) of coarc-

21. Robb, G. P., and Steinberg, I.: Visualization of the Chambers of the Heart, Pulmonary Circulation and Great Blood Vessels in Man: Summary of Method and Results, J. A. M. A. **114**:474 (Feb. 10) 1940.

22. Wolke, K.: Two Cases of Coarctation (Stenosis of the Isthmus) of the Aorta, Acta radiol. **18**:319, 1937.

23. King, J. T., Jr.: Stenosis of the Isthmus (Coarctation) of the Aorta and Its Diagnosis During Life, Arch. Int. Med. **38**:69 (July) 1926.

24. Eisenberg.[4x] Eisenberg and Gibson.[5f]

25. Appelbaum, E., and Kalkstein, M.: Coarctation of the Aorta: Report of a Case with Associated Anomalies, Ann. Int. Med. **12**:550 (Oct.) 1938.

26. Master, A. M.: The Electrocardiogram and X-Ray Configuration of the Heart, Philadelphia, Lea & Febiger, 1939.

27. Graybiel, A., and White, P. D.: Electrocardiography in Practice, Philadelphia, W. B. Saunders Company, 1941.

28. Schnitker, M. A.: The Electrocardiogram in Congenital Cardiac Disease, Cambridge, Mass., Harvard University Press, 1940.

tation in which electrocardiograms were taken. Only 32 of the electrocardiograms were normal. Of the 84 abnormal electrocardiograms, there were 57 with a left axis deviation and 8 with a right axis deviation. In 17 the QS interval was over 0.10 second. In 14 others various abnormalities, such as high or low take-off of the ST interval, inverted T wave, notched or inverted P wave or notched or biphasic QRS complex, were noted. From this it would seem that the chance of finding an abnormal electrocardiogram in a case of coarctation of the aorta is about 2½ to 1; the chance of finding left axis deviation is even.

The findings in children do not vary materially: Of 30 children for whom electrocardiograms were taken, 13 had a left axis deviation, 2 had a right axis deviation, 5 had some other abnormality and 10 were considered normal.

In 3 of 4 cases of coarctation with right axis deviation and a normal conduction time autopsy was not performed. However, one of the patients (a boy of 9 years reported on by Schwartz and Greene [5h]) had a greatly dilated pulmonary artery revealed by roentgen examination and a "machinery" murmur, indicating a patent ductus arteriosus. Also reported in the literature were 4 cases of coarctation with right axis deviation and a QS interval of 0.10 second or over. One of the patients (case 22 of Schnitker,[28] reported by Rösler and Kiss in 1931) had a moderately patent ductus arteriosus. Another (Ulrich's [29] case 3) had a patent ductus arteriosus and a bilaterally hypertrophied heart, weighing 870 Gm. The patient of Narr and Wells [30] had left ventricular hypertrophy and dilatation and that of Kellogg and Biskind [31] left ventricular hypertrophy with a ductus arteriosus patent to a bristle.

It would seem, therefore, that right axis deviation frequently, but not always, accompanies a patent ductus arteriosus. Left ventricular hypertrophy apparently without other abnormalities has been found ir subjects with right axis deviation.

We are at a loss to explain the right axis deviation in case 1 except on the basis of extreme left ventricular hypertrophy with a change in the pattern of intraventricular conduction, or on the basis of some coexistent congenital lesion that has caused a right ventricular enlargement. Usually, the higher amplitudes accompany left ventricular enlargement.

Prognosis.—The cause of death in 155, or 77 per cent, of the 200 cases with autopsy analyzed by Abbott [10] was the coarctation or a com-

29. Ulrich, H. L.: Coarctation of the Aorta (Adult Type): A Report of Three Cases, Am. Heart J. **7**:641 (June) 1932.

30. Narr, F. C., and Wells, A. H.: Rupture of the Aorta, Am. Heart J. **8**: 834 (Aug.) 1933.

31. Kellogg, F., and Biskind, G. R.: Coarctation of the Aorta, Anomalous Coronary Artery and Patent Ductus Arteriosus, California & West. Med. **40**:368 (May) 1934.

plicating cardiac lesion. Noteworthy was the large number of cases of sudden and spectacular death due to rupture of the aorta, to rupture of a cerebral aneurysm or without apparent cause. Blackford [1] emphasized that many of the victims of this condition were young athletes who died during or shortly after exercise; he felt that their normal life expectancy might have been attained if all unusual strain on the cardiovascular system had been removed. He also advocated the removal of foci of infection to reduce the danger of bacterial endocarditis or endarteritis. In that connection Sangster [32] stated that excessive hemorrhage is likely to follow extraction of teeth or tonsillectomy; however, tonsils have been removed from at least 7 children (including K. G. and G. M., in our cases 1 and 3) with no mention of hemorrhage. The danger of bacterial invasion is probably much greater than that of hemorrhage.

Thus, it would seem important to diagnose coarctation as early in childhood as possible. As Blackford stated: "After symptoms of cardiac failure appear it is too late to advise the patient that he may have a better chance of avoiding cardiac failure or rupture of a vital vessel."

SUMMARY

A review of the literature on coarctation of the aorta revealed 47 cases in which the adult type had been diagnosed during life in children under 15 years of age. It is important to make the diagnosis of coarctation as early in childhood as possible, since the life of the patient may be prolonged by prohibiting strenuous sports and occupations.

When coarctation of the aorta is pronounced enough to give clinical signs, its diagnosis is not difficult if the condition is kept in mind. It should be suspected when forceful pulsations in the neck and hypertension, particularly with a wide pulse pressure, are observed in a child. The presence of a much lower blood pressure in the lower extremities and of retardation and diminution of pulsation in the femoral arteries confirms the diagnosis. The finding of a collateral circulation and the roentgenologic signs are valuable aids.

If routine determinations of blood pressure in children are made on only one arm, the right arm should be used, in order to avoid overlooking the occasional cases of coarctation in which the pressure is low in the left arm. Such a case is reported, together with interesting electrocardiographic observations.

32. Sangster, C. B.: Coarctation of the Aorta, with Report of a Case, M. J. Australia **1**:733 (May 15) 1937.

Correspondence

SPECIFIC ANTISERUM AGAINST RICIN

To the Editor:—On pages 485 and 486 of the September 1942 issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, under the heading "Case Reports," there is an article by Koch and Kaplan entitled "Castor Bean Poisoning." In the last paragraph the authors state that there is no specific antidote for this condition. They further state that the mortality in a series of 150 cases was 6 per cent.

As it is perfectly feasible to make an antiserum against the toxin, ricin, by inoculating rabbits with increasing doses of ricin, should not steps be taken by some society to induce one of the companies manufacturing biologicals to prepare this specific antiserum and have the fact that this exists publicized, so that it may be used in future cases of castor bean poisoning? It would seem logical that the mortality rate could thus be reduced to a minimum. I suppose that ricin could be manufactured by any one desirous of so doing. In 1935-1936, while experimenting with this material at the School of Hygiene of the University of Toronto, I used material which had been prepared by Schuardt.

A. E. ALLIN, M.D., D.P.H.

Director of the branch laboratory, Ontario Department of Health, Fort William, Ontario, Canada.

News and Comment

GENERAL NEWS

American Board of Pediatrics.—The American Board of Pediatrics announces that on July 1, 1943, Group I (physicians who have specialized in pediatrics for ten years or more) will be abolished.

Physicians Certified by American Board of Pediatrics.—The following physicians were certified as specialists by the American Board of Pediatrics at the meeting at Chicago on Nov. 1, 2 and 3, 1942:

Dr. John Milton Adams, Minneapolis; Dr. J. Roberto Aguayo, Caguas, Puerto Rico; Dr. Julius Aronow, Chicago; Dr. J. E. Bacon, Dubuque, Iowa; Dr. J. Joseph Baratz, Chicago; Dr. James Frazier Binns, Nashville, Tenn. (in the Army); Dr. Lawrence Breslow, Chicago (in the Army); Dr. Edward William Bulley, Vicksburg, Miss.; Dr. M. C. Carlisle, Waco, Texas; Dr. Willie Mae Clifton, Chicago; Dr. Martha Eleanor Cook, Lake Charles, La.; Dr. Jacob Adolph Danciger, Memphis, Tenn. (in the Army); Dr. William Deering, Chicago (in the Army); Dr. Sol Paul Ditkowsky, Normal, Ill. (in the Army); Dr. James W. DuShane, Evanston, Ill.; Dr. O. E. Ehrhardt Springfield, Ill. (in the Army); Dr. Lucas W. Empey, Roseville, Calif.; Dr. Dorothy F. Falkenstein, Columbus, Ohio; Dr. Robert Raines Harriss, Hollywood, Fla.; Dr. Frank Dickerson Hazlett, Washington, Pa. (in the Army); Dr. Herbert Kahan, New Rochelle, N. Y. (in the Army); Dr. Herschell Jerome Kaufman, Port Arthur, Texas (in the Army); Dr. William White Kelton, Jr., Austin, Texas; Dr. Ernest R. Kimball, Jr., Chicago (in the Army); Dr. Joseph M. Klein, Wilkes-Barre, Pa. (in the Army); Dr. George John Klok, Council Bluffs, Iowa (in the Navy); Dr. John Sanford Kruglick, Chicago (in the Army); Dr. Harry J. Lefkowitz, Cleveland (in the Army); Dr. Edward Louis Levert, New Orleans; Dr. Lavinia Gould MacKaye, Ann Arbor, Mich.; Dr. Herman Braun Marks, Pawtucket, R. I. (in the Navy); Dr. Eva Linn Meloan, Jackson, Miss.; Dr. Betty Moody, Houston, Texas; Dr. William B. Mullins, Shawnee, Okla.; Dr. Richard Leedom Nelson, Wichita Falls, Texas; Dr. R. A. Norton, Tacoma, Wash. (in the armed forces); Dr. Emanuel Padnos, Chicago; Dr. Ralph V. Platou, New Orleans; Dr. Alice Potter, San Francisco; Dr. W. Pierre Robert, Beaumont, Texas; Dr. Burton Rosenholtz, St. Paul, Minn.; Dr. William David Rothwell, Denver; Dr. Joseph D. Russ, New Orleans (in the Army); Dr. Thomas J. Senese, Gary, Ind.; Dr. Miner W. Seymour, Columbus, Ohio (in the Army); Dr. Arthur L. Shafton, Chicago; Dr. Noel G. Shaw, Evanston, Ill.; Dr. J. Sam Smith, Montgomery, Ala.; Dr. Elaine Moore Thomas, Chicago; Dr. John Martin Thomas, Omaha; Dr. William Clifford Vance, Richmond, Ind. (in the Army); Dr. Dorothy Fraser Wheeler, Fresno, Calif.; Dr. Edward Marion Wier, Fort Worth, Texas; Dr. Alvin B. Williams, San Jose, Calif. (in the Army); Dr. Hillard Wood Willis, Coral Gables, Fla.; Dr. David B. Witt, Alexandria, La. (attached to the Army); Dr. Carl Witus, Detroit (in the Army); Dr. Louise A. Yeazell, San Francisco; Dr. Edward William Zeman, Hibbing, Minn.; Dr. Helen Jane Zillmer, Milwaukee, Wis.

Georgia Pediatric Society.—The Georgia Pediatric Society will hold its annual scientific meeting in Atlanta, Ga., Dec. 10, 1942. The afternoon session will be at the Pompeian Ball Room, Biltmore Hotel, and the evening session at the main auditorium, Academy of Medicine, Fulton County Medical Society.

The following are the speakers and their subjects:

Alexander Ashley Weech, M.D., B. K. Rachford Professor of Pediatrics, University of Cincinnati; Medical Director of the Children's Hospital Research Foundation, Cincinnati: (1) Significance of Protein in the Diet; (2) Cortical Maturation and Development of Behavior in Infants.

Meredith Campbell, M.D., Professor of Urology, New York College of Medicine, New York: (1) Persistent Urinary Infection in the Young; (2) Surgical Treatment of Certain Common Urologic Conditions in Children.

Abraham Levinson, M.D., Assistant Professor of Pediatrics, Northwestern University Medical School; Professor of Pediatrics, Cook County Graduate School, Chicago: (1) Neurologic Disturbances of the Newborn; (2) Value and Limitations of Spinal Puncture in Children.

DEATHS

Dr. LeRoy A. Wilkes, Trenton, N. J., Executive Officer of the Medical Society of New Jersey and formerly Medical Director of the American Child Health Association, died suddenly at Trenton, N. J., Nov. 29, 1942. Dr. Wilkes had long been engaged in activities in connection with child health and medical organizations, and his loss will be greatly felt, not only by his friends but by those who are interested in the welfare of children in the United States.

Dr. Howard B. Mettel, Director of Maternity and Child Health with the Indiana State Board of Health, died Nov. 30, 1942, of an intestinal disturbance, at the Barnes Hospital in St. Louis. Dr. Mettel was a progressive and active man in his work, and his loss will be much felt in Indiana and by his colleagues generally throughout the United States.

Obituaries

HORTON CASPARIS, M.D.

1891–1942

The friends and associates of Dr. Horton Casparis were shocked to receive the news of his death on Nov. 12, 1942, in Richmond, Va., where he was attending the meeting of the Southern Medical Association.

Dr. Casparis was born at Round Mountain, Texas, on March 13, 1891. He received his early schooling in Texas and graduated with an A. B. degree from the University of Texas in 1915. He received the degree of Doctor of Medicine at the Johns Hopkins University Medical School in 1919. For the year 1919-1920 he was obliged to interrupt his regular educational program and enter Trudeau Sanatorium, Trudeau, N. Y., at first as a patient and later as part time member of the staff. The year at Trudeau restored his health and aroused his interest in the fight against tuberculosis. From 1920 to 1924 Dr. Casparis served in the various capacities of assistant resident, resident, instructor and associate in the department of pediatrics at the Johns Hopkins Hospital. Here he demonstrated keen clinical insight and good judgment in handling disease in children. He had a remarkable ability of gaining a child's confidence and making him feel that his doctor was his friend.

After a year spent at various European clinics, Dr. Casparis was called in 1925 to head the division of pediatrics, then a part of the department of medicine, in the newly organized Medical School at Vanderbilt University, Nashville, Tenn. In 1928 pediatrics was made an independent department, and Dr. Casparis became professor and pediatrician in chief. From humble beginnings with limited space and facilities he developed an active department with diversified interests and well balanced emphasis on the care of sick children, the teaching of pediatrics and clinical and scientific research.

Dr. Casparis' energy and enthusiasm were not, however, to be confined within the limits of his own department. His interest in tuberculosis made him eagerly meet the challenge offered by the high incidence of tuberculosis in Tennessee. He early set to work on the problems involved in organizing a successful fight against the disease. That he served as president of the Southern Conference and on the board of directors and executive committee of the National Tuberculosis Association is evidence of the recognition of his ability in this field. At the

time of his death he was director of the National Tuberculosis Association, president of the Tennessee Tuberculosis Association, member of the council of the American Trudeau Society and president of the southern branch of the society.

Dr. Casparis grew to be chiefly interested in all the broad aspects of the welfare of children. To him pediatrics meant prevention as well as treatment of disease, adequate nutrition, education calculated to

HORTON CASPARIS, M.D.
1891–1942

enable a child to meet the problems of life, mental health and a wholesome social environment. There was almost no field of effort pertaining to any phase of the care and training of children to which he did not contribute a generous measure of his time and energy. His easy, genial manner and understanding of human nature made it possible for him to win enthusiastic support and cooperation from a wide variety of individuals and organized groups. He was in constant demand as a

speaker at clinical and scientific meetings and before civilian groups interested in the welfare of children. In addition to his connection with the tuberculosis associations already mentioned, he served as chairman of the pediatric section of both the Southern and the American Medical Association. At the time of his death he was president of the American Board of Pediatrics, member of the editorial board of the *American Journal of Diseases of Children,* president of the Nashville Public Health Nursing Council, member of the advisory panel of the National Association of Nursery School Education, a member of the National Maternal and Child Health Council, chairman of the advisory committee of the United States Children's Bureau, a member of the mental health committee of the American Academy of Pediatrics, member of the National Commission for Young Children and chairman of the Tennessee State Nutrition Committee.

Death came to Dr. Casparis at the peak of his active career, long before he had reached many of the goals in child welfare he had hoped to achieve. Nevertheless, his contributions to the fundamental groundwork, together with the momentum imparted by his abundant and contagious enthusiasm, will long continue to inspire others in many fields.

K. D.

Abstracts from Current Literature

Vitamins; Avitaminoses

ORAL LESIONS ASSOCIATED WITH DIETARY DEFICIENCIES IN MONKEYS. O. D. CHAPMAN and A. E. HARRIS, J. Infect. Dis. **69**:7 (July-Aug.) 1941.

Unlike normal monkeys, monkeys maintained on certain vitamin-deficient diets tend to have oral lesions associated with an increase in the fusospirochetal flora. The author made a few observations which would seem to indicate that monkeys maintained on diets deficient in the vitamin B_2 (or G) complex, except B_6, plus supplements of vitamins A, D, C, nicotinic acid (niacin) and riboflavin tend to acquire rather severe oral lesions and severe general symptoms and have short survival times. Monkeys maintained on an adequate stock diet tend to resist artificial implantation of the fusospirochetal flora under the severest of test conditions.

TOOMEY, Cleveland.

Hygiene; Growth and Nutrition; Public Health

STUDIES IN CHILDBIRTH MORTALITY: III. PUERPERAL FATALITY IN RELATION TO MOTHER'S PREVIOUS INFANT LOSSES. JACOB YERUSHALMY, ELIZABETH M. GARDINER and CARROLL E. PALMER, Pub. Health Rep. **56**:1463 (July 18) 1941.

Of the 161,177 births of second-born or later-born children entering into this study, 76.9 per cent were to mothers whose previous issue had all survived and 23.1 per cent were to mothers who had lost one or more previous children. The rate of loss of both mother and infant was about twice as high for the group with a history of previous loss as for the group with no previous loss. The higher the number of previous losses to the mother, the greater was the chance of death to both mother and infant. This observation cannot be explained on the basis of differences in parity or age of the mother. It was associated with premature as well as with full term deliveries. The previous losses to the mothers were found to be more closely related to loss of offspring than to loss of mother. The suggestion is made that the father may also play an important part in these repeated losses in the family.

SANFORD, Chicago.

THE PUBLIC HEALTH NURSE IN SCHOOLS. MARÍA ANTONIETA DE CASTRO, Bol. Inst. internac. am. de protec. a la infancia **15**:5 (July) 1941.

The author emphasizes the importance that the function of the school nurse has in relation to the pupils' health, especially where there is an adequate cooperation between the school nurse, the headmaster and the staff of the school.

EDITOR'S SUMMARY.

SOCIAL ASSISTANCE TO THE HANDICAPPED. ABRAHAM GRIMBERG V., Bol. Inst. internac. am. de protec. a la infancia **15**:19 (July) 1941.

As a conclusion, the author suggests that the first American Congress for Special Training should agree to recommend that all the governments of the American countries assist the handicapped. For such purpose an organization should be established to train the handicapped child culturally and professionally, to support him in the fulfilment of his work and to facilitate his fitness for social life, thus making possible for him a life of dignity and tranquility, which he deserves.

AUTHOR'S CONCLUSION.

EDUCATIONAL MEASURES. EMILIO VERDESIO, Bol. Inst. internac. am. de protec. a la infancia **15**:32 (July) 1941.

The author advocates a technic for measuring educational accomplishment. The details are not given in the English summary. LESLIE, Evanston, Ill.

Prematurity and Congenital Deformities

FETAL ELECTROCARDIOGRAPHY. H. MANN and P. BERNSTEIN, Am. Heart J. **22**:390 (Sept.) 1941.

Fetal electrocardiograms obtained by a special technic utilizing abdominal leads were satisfactory in 90 per cent of tracings made during the last trimester of pregnancy.

No obvious relationship between fetal and maternal heart rates can be demonstrated. Congenital heart disease or other anomalies cannot be revealed by fetal electrocardiography.

In some instances fetal distress or death in utero can be diagnosed and fetal arrhythmias and the effect of drugs on fetal heart rate can be accurately studied.

GIBSON, Chicago.

SECONDARY REPAIR OF CLEFT LIPS AND THEIR NASAL DEFORMITIES. JAMES BARRETT BROWN and FRANK MCDOWELL, Ann. Surg. **114**:101 (July) 1941.

Secondary repair of cleft lips and their nasal deformities may be required even though a good primary repair in infancy has been obtained, and there is little reason for any one's going through life with a noticeable deformity without having some attempt made for its correction. The authors discuss methods of preventing deformity and describe in detail secondary repair.

BANTIN, Omaha.

Acute Contagious Diseases

ARE PRESENT DAY QUARANTINE METHODS ARCHAIC? ARCHIBALD L. HOYNE, Illinois M. J. **80**:205 (Sept.) 1941.

Dr. Hoyne believes that the usual quarantine regulations for the control of the common contagious diseases have been an utter failure. Patients with a contagious disease and susceptible contacts should be isolated. In most instances, placarding of premises has no scientific value if the family concerned possesses average intelligence and if the home is visited at proper intervals by a field nurse or health officer. Infectious disease hospitals should be maintained primarily for those patients who require hospital treatment. Satisfactory control is possible only for those of the common contagious diseases for which an efficient immunizing agent is available.

BARBOUR, Peoria, Ill.

SUSCEPTIBILITY TO PARALYSIS IN POLIOMYELITIS. W. LLOYD AYCOCK, Illinois M. J. **80**:231 (Sept.) 1941.

The occurrence of paralysis among persons exposed to the virus of poliomyelitis is limited, irregular and selective. A number of these selectivities suggest that the major determinant lies in the host rather than in parasitic factors. The inherent susceptibility seems to lie in some physiologic process which fluctuates with climate and season, rather than in a fixed anatomic character. This underlying physiologic factor may be subclinical and endocrine in nature. It may be that alteration in the nasal mucosa, which may affect susceptibility, is the result of an inherent fault in physiologic function which has to do with the economy of estrogenic substances.

BARBOUR, Peoria, Ill.

STUDIES ON MEASLES: III. THE USE OF TISSUE CULTURE IN PROPAGATION OF MEASLES VIRUS. GEOFFERY RAKE, MORRIS F. SHAFFER and HELEN P. JONES, J. Infect. Dis. **69**:65 (July-Aug.) 1941.

These authors claim to have propagated the agent of measles, obtained from nasopharyngeal washings of human patients, by serial passages in tissue culture according to the method of Plotz for at least ten passages. The presence of the agent has been demonstrated by inoculation of the tissue culture material into Macaca mulatta monkeys with the production of characteristic measles.

The ability of the virus of measles to withstand treatment with 10 per cent anesthetic ether for thirty minutes at room temperature had been confirmed. The successful propagation of the virus of measles on the chorioallantois of the chicken embryo for at least thirty serial passages has also been confirmed.

TOOMEY, Cleveland.

STUDIES ON THE INACTIVATION OF DIPHTHERIA TOXIN BY VITAMIN C (1-ASCORBIC ACID). CLAUS W. JUNGEBLUT, J. Infect. Dis. **69**:70 (July-Aug.) 1941.

In vitro inactivation of diphtheria toxin by vitamin C occurs as a result of direct interaction between the two substances.

This inactivation does not follow the laws of multiple proportions and is limited to comparatively small doses of toxin and ascorbic acid.

Detoxification is enhanced by the presence of an excess of cupric ions in toxin–ascorbic acid systems, which suggests that the toxin is inactivated during the auto-oxidation of ascorbic acid. The substance responsible for this inactivation seems to be a peroxide.

Administration of vitamin C may occasionally protect guinea pigs against intoxication with a lethal dose of toxin but fail to make subtherapeutic doses of antitoxin effective. Neither vitamin C nor vitamin B_1 has any demonstrable effect on the development or on the course of postdiphtheritic paralysis in guinea pigs.

TOOMEY, Cleveland [AUTHOR'S SUMMARY].

PERTUSSIS PROPHYLAXIS WITH TWO DOSES OF ALUM-PRECIPITATED VACCINE. JOSEPH A. BELL, Pub. Health Rep. **56**:1535 (Aug. 1) 1941.

Bell reports that two 1 cc. doses of alum-precipitated pertussis vaccine injected with a four-week interval between doses into a large proportion of a group of children in Norfolk, Va., conferred real protection against clinical attacks of pertussis.

SANFORD, Chicago.

MUMPS MENINGOENCEPHALITIS. A. W. FRANKLAND, Brit. M. J. **2**:48 (July 12) 1941.

This article is a brief review of 234 cases of mumps observed in a recent epidemic of mumps among soldiers. Because of a previous epidemic of meningococcic meningitis the majority of these patients were sent to the hospital with a tentative diagnosis of meningitis. In 5 of the patients the symptoms were severe enough to justify a lumbar puncture, and in all of them pleocytosis was found. Of the patients reported on in this article 30 per cent had signs and symptoms of meningeal involvement. In the five cases in which lumbar punctures were done the cell count varied between 230 and 1,078. In 3 of these 5 cases sulfapyridine was administered. Vomiting, headache and depression were made worse by the drug therapy, and recovery was delayed. After this all patients were treated mainly symptomatically and given copious fluids.

The author comments that in this described epidemic the number of cases of mumps with complications was high. Of all patients admitted to the hospital 30 per cent had signs and symptoms of meningeal involvement. It was thought that the virus responsible for the infection was probably of a neurotropic type.

ROYSTER, University, Va.

A Note on the Cultivation of Hemophilus Pertussis. P. M. Anderson, M. J. Australia **2**:224 (Aug. 30) 1941.

By the use of postnasal swabs taken through the anterior nares from patients with whooping cough Anderson was able to obtain a satisfactory proportion of positive cultures. A comparison with the cough plate method was not made. The swab method is more satisfactory than the cough plate method when one is dealing with infants, with patients in whom the cough is weak and with patients with milder suspected conditions in which the cough occurs chiefly at night.

Gonce, Madison, Wis.

Acute Infectious Diseases

The Blood Picture in Rheumatic Fever. V. P. Wasson, E. E. Brown and C. Weintraub, Am. Heart J. **22**:342 (Sept.) 1941.

Determination of the erythrocyte sedimentation rate is the most delicate means of determining the presence or absence of active infection in rheumatic fever. Determination of the nonfilamented neutrophil count is less delicate, but it should be used routinely on all patients with rheumatic fever, inasmuch as an increase in the number of nonfilamented forms indicates the presence of infection. The capillary resistance test ranks third in diagnostic importance, erythropermeability being usually increased in rheumatic fever, especially during the active phase of the disease. Blood platelets were found to be fewer than 200,000 per cubic millimeter in two thirds of the patients. Hemoglobin estimation is not important as an isolated test. Coagulation and bleeding times are not significantly altered in rheumatic fever.

Gibson, Chicago.

The Diagnostic and Epidemiologic Significance of the Complement Fixation Test in Human Malaria. I. J. Kliger and M. Yoeli, Am. J. Trop. Med. **21**:531 (July) 1941.

The authors examined serums from over 300 patients with malaria taken at various intervals following an attack.

Using the antigen as prepared by Coggeshall, they found specific positive complement fixation reactions with dilutions of 1:160 and 1:320. The time of appearance and the concentration of the antibody responsible for the reaction varied with the number of attacks. As a rule, the reaction became positive during the third week provided the patient had had two or more attacks. Patients cured after one attack failed to give positive reactions. The reactions usually disappeared again during the fourth month following the last attack.

Mass tests carried out in hyperendemic areas showed that 98 per cent of the serums of children up to the age of 12 years gave positive reactions, whether or not they showed a blood infection at the time of the test. Infected adults in this area gave similar results. Healthy adults gave only 10 per cent positive reactions. Treated persons gave positive or negative reactions according to the interval between the last attack and the date of treatment.

They concluded that the reaction may prove useful for epidemiologic purposes.

Burpee, Augusta, Ga.

The Use of Bovine Antitoxin for the Prophylaxis of Tetanus. Jerome Glaser, J. Allergy **12**:537 (Sept.) 1941.

The author reports his experience in the use of bovine tetanus antitoxin for 38 patients, ranging in age from 1.5 to 18 years.

He believes that it should be used in preference to the equine tetanus antitoxin in prophylactic doses, especially when skin testing has shown the patient to be sensitive to horse serum. Generalized reactions which were not severe occurred in 5.1 per cent of his cases.

Hoyer, Cincinnati.

ANIMAL INOCULATION WITH PURE CULTURES OF TRICHOMONAS VAGINALIS AND TRICHOMONAS FOETUS. RAY E. TRUSSEL and S. H. MCNUTT, J. Infect. Dis. **69**:18 (July-Aug.) 1941.

Vaginal inoculations of Trichomonas vaginalis in bacteria-free cultures were successful only in Macacus rhesus monkeys. (This same strain has been used to produce vaginitis in human beings.) Trichomonas foetus could be implanted in cattle and for very brief periods in dogs. Sheep, swine, horses, goats, guinea pigs, rabbits and cats could not be infected vaginally with either trichomonad.

Oral inoculations with T. vaginalis in chickens, turkeys, mice and pigeons were unsuccessful. T. foetus could not be implanted by the oral route in chickens, turkeys and pigeons.

Rectal inoculations of chickens and turkeys with T. vaginalis were unsuccessful, and T. foetus could not be implanted rectally in turkeys.

Subcutaneous inoculations of both organisms in guinea pigs were without effect.

Intraperitoneal inoculations of turkeys, guinea pigs, and mice with T. foetus gave negative results, as did similar inoculations of turkeys and guinea pigs with T. vaginalis.

Intravenous inoculations of cattle, dogs and rabbits with both organisms were without apparent effect.

Intracranial inoculations of calves, guinea pigs and rabbits were equally negative.

Both T. vaginalis and T. foetus were successfully cultured in chick embryos, although this was more difficult with T. vaginalis.

TOOMEY, Cleveland [AUTHORS' SUMMARY].

DETERMINATION OF THE ACTIVITY OF VARIOUS DRUGS AGAINST THE MALARIA PARASITE. L. T. COGGESHALL and JOHN MAIER, J. Infect. Dis. **69**:108 (Sept.-Oct.) 1941.

A method has been described for the evaluation of potential antimalarial drugs by determining their inhibitory effect on the respiration of the parasite in vitro.

The inhibitory effect is expressed as a coefficient which is standardized so that the activities of various drugs may be compared.

Data have been presented which show that the effect of nine different drugs on the respiration of malaria parasites in vitro cannot uniformly be correlated with the response of the host in experimental malaria infections with five species of plasmodia.

Therefore, it is concluded that inhibition of respiration in vitro alone should not be depended on to furnish an index of chemotherapeutic efficiency but should be used as an adjunct to in vivo experiments.

TOOMEY, Cleveland [AUTHORS' SUMMARY].

THE TREATMENT OF A GROUP C STREPTOCOCCUS INFECTION IN GUINEA PIGS WITH VITAMIN C AND SULFANILAMIDE. LEONARD KAREL, THOMAS C. GRUBB and C. W. CHAPMAN, J. Infect. Dis. **69**:125 (Sept.-Oct.) 1941.

In 160 guinea pigs infected with a group C streptococcus, the course of the infection and the effectiveness of sulfanilamide were studied in relation to the vitamin C content of the animals. Thirty-one noninfected animals with a normal or low vitamin C content were included as controls.

The weighted mean survival times for the various groups of guinea pigs were determined at the end of fourteen days (three hundred and thirty-six hours) of observation.

Sulfanilamide was effective in the treatment of a group C streptococcus infection in guinea pigs, but neither high ascorbic acid content nor ten days of vitamin C depletion influenced the effect of sulfanilamide.

In the absence of sulfanilamide treatment, the course of the infection as measured by survival time was not influenced either by high ascorbic acid content or by ten days of vitamin C depletion.

TOOMEY, Cleveland [AUTHORS' SUMMARY].

THE PULSE RATE IN ACUTE JUVENILE RHEUMATISM.. A. J. GLAZEBROOK and SCOTT THOMSON, Edinburgh M. J. **48**:619 (Sept.) 1941.

Observations were made on the pulse rate in 100 consecutive cases of acute rheumatism in boys and youths from 15 to 20 years old. The period of observation was confined to the first four weeks of the illness, since all the patients had a tachycardia in the later stages of the disease. The study dwells on the nature of bradycardia, which is a common feature of the first attack of rheumatism occurring in young adolescents. This depression of the pulse rate was found at an early stage of the rheumatism and was often transient. Bradycardia was seen in patients with the disease in every degree of severity. It is of grave prognostic significance for permanent cardiac damage and may be due to the action of streptococcus endotoxins.

NEFF, Kansas City, Mo.

TRICHINIASIS. PAUL B. BEESON, Lancet **2**:67 (July 19) 1941.

The clinical features of trichiniasis are discussed, attention being directed to the variability of the disease, both in the nature of its manifestations and in the severity in different subjects.

An eosinophil count is the best guide to early diagnosis. The parasites can sometimes be isolated from the blood during the early weeks of infection. They can usually be found in muscle tissue after the third week. The specific cutaneous test and precipitin reaction with trichinella antigen are useful diagnostic procedures under certain conditions.

LANGMANN, New York.

BLOOD PICTURE IN TRICHINIASIS. B. L. DELLA VIDA and S. C. DYKE, Lancet **2**:69 (July 19) 1941.

The blood picture of 100 patients was studied. Leukocytosis occurred in a primary wave, reaching its peak at about the third week from onset of symptoms, and a secondary wave, reaching its peak at the eleventh week.

The eosinophils diminished in number or disappeared within the first three days from onset of symptoms; thereafter they increased in primary and secondary waves coinciding with those of the general leukocytosis.

The number of neutrophils diminished during the waves of general leukocytosis and increased as the eosinophilia diminished.

The monocytes increased with the first decrease of the eosinophilia.

LANGMANN, New York.

BACTERIOLOGY OF SALMONELLOSIS. IVAN SAPHRA, Arch. de med. inf. **10**:143 (July-Sept.) 1941.

This was an address given at the joint session of the Cuban Pediatric Society and the Cuban Society of Microbiology. Saphra gives an explanation of the complex problem of the serologic classification of the organisms of the Salmonella group.

SANFORD, Chicago.

THE CLINICAL ASPECT OF SALMONELLOSIS. ANGEL A. ABALLI, Arch. de med. inf. **10**:158 (July-Sept.) 1941.

The author is professor of pediatrics in the University of Havana School of Medicine. This lecture treats the seriousness and frequency of Salmonella infections in the municipal hospital in Habana, Cuba. Nine case histories are given as examples. Aballi believes that more frequent bacteriologic examination will show a greater frequency of the infection.

SANFORD, Chicago.

Chronic Infectious Diseases

PRESENT STATUS OF THE TUBERCULIN PATCH TEST. CAMILLE KERESZTURI, Am. Rev. Tuberc. **44**:94 (July) 1941.

In the published studies on the subject of the reliability of the tuberculin patch test compared with that of intracutaneous tests with old tuberculin and with purified protein derivatives, Kereszturi considers that only 9 of 19 reports furnish data sufficient for accurate appraisal. Among her criticisms were variations in the strength of the tuberculin used and differences in interpretation of the reactions. Some investigators dealt with adults and some with children; some with institutional known reactors and some with the general population. There were also differing methods of computation which made comparisons difficult. These reports are critically considered and compared with her own studies on the subject. From the combined data of comparable studies she finds that 15 per cent of subjects who gave positive Mantoux reaction have exhibited a negative reaction to a patch test, and that 3 per cent of subjects with a negative Mantoux reaction have given a positive reaction to a patch test. In her own studies she found that 27 per cent of subjects with a positive Mantoux reaction exhibited a negative reaction to a patch test while 11 per cent of subjects with a negative Mantoux reaction gave a positive reaction to a patch test. She admits that most of the discordant results were obtained from subjects who exhibited slight or dubious reactions to tuberculin; also that the patch test is capable of giving highly reliable results when performed under ideal conditions. However, the evidence so far available does not indicate that the patch test can be used to replace in reliability the well established Mantoux test.

EUGENE SMITH, Ogden, Utah.

FREQUENCY OF TUBERCULOUS LESIONS AT AUTOPSY. KURT E. LANDÉ and GEORGE WOLFF, Am. Rev. Tuberc. **44**:223 (Aug.) 1941.

The postmortem examinations reported on were made over a period of two years in a general hospital located in a semirural community which had been selected as typical for other surveys by the United States Public Health Service. Of 176 autopsies performed, 165 were considered suitable for this study; among these there were 65 (39.4 per cent) with reports of tuberculous findings. Thirty-two of these examinations were performed on infants and children up to 10 years of age, of whom 21 were under 1 year of age. By age groups the percentage of positive results were: birth to 19 years, 37, or 8.1 per cent; 20 to 49 years, 49, or 42.5 per cent; 50 years and over, 45, or 51.1 per cent.

On the basis of these observations compared with those of previous investigations in Europe and the United States, it may be assumed that the number of persons infected and pathologically marked by tuberculosis among an unselected hospital population has been reduced from almost 100 per cent at the turn of the century to about 50 per cent at present.

EUGENE SMITH, Ogden, Utah.

THE ACTINOMYCES OF THE HUMAN MOUTH. BASIL G. BIBBY and HOLMES T. KNIGHTON, J. Infect. Dis. **69**:148 (Sept.-Oct.) 1941.

A review of the reports of isolation of branched organisms from the normal human mouth indicated that confusion has occurred between the actinomycetes and other filamentous mouth bacteria and also between actinomycetes from the mouth and those from extraneous sources. Studies of smears failed to demonstrate the presence of branched filaments. Cultural experiments revealed numbers of irregular branched and clubbed, readily fragmenting aerobic organisms. Similar anaerobic types were occasionally found. Classification of the thirty-five strains surviving in subcultures was not possible, but morphologic similarity of the aerobic organisms to Actinomyces bovis was noted.

TOOMEY, Cleveland [AUTHORS' SUMMARY].

FALSE POSITIVE SEROLOGIC TESTS FOR SYPHILIS IN CHILDREN. MORRIS L. BRIDGEMAN and LEONARD D. JACOBSON, Northwest Med. **40**:325 (Sept.) 1941.

Bridgeman and Jacobson assert that there have been a greater number of false positive reactions to tests for syphilis in recent years, which may be due to the increased sensitivity and lessened specificity of the newer flocculation and precipitation tests.

In children, a false positive biologic reaction is most often associated with an acute infectious process with an elevation of temperature. Because of this it would be advisable to wait for a normal temperature before doing serologic tests.

It is entirely conceivable that, because of the nonspecific nature of the serologic tests, pathologic processes other than the spirochetal diseases can liberate a reagin-like substance which will give false positive reactions. Conditions reported as most commonly doing this are leprosy, malaria, infectious mononucleosis, trypanosomiasis, septicemia, scarlet fever, tuberculosis, jaundice, acute febrile conditions of varying nature, diabetes and varicella. Also it has been shown that false positive biologic reactions occur in a certain small percentage of perfectly normal persons showing no evidence of the presence of any infectious process.

Before a label of syphilis is placed on any child, and more important, before treatment is instituted, care should be taken to establish a definite diagnosis, by such criteria as: (*a*) positive physical findings in the child; (*b*) a definite history from either of the parents; (*c*) in the absence of these evidences serologic tests with persistently positive reactions over a period of several weeks and rechecked by several different methods by different laboratories (the practice of beginning treatment on the sole basis of two, three or even four positive tests is to be condemned; the value of the spinal serologic tests as confirmatory evidence is recognized, but false positive reactions can occur with the spinal fluid); (*d*) ruling out by the proper laboratory procedures of the presence of the more common diseases known frequently to cause false positive reactions, such as malaria and especially infectious mononucleosis, and (*e*) the use of Kahn's verification test as a possible aid in segregating the false from the true positives.

The value of the various serologic tests used to diagnose syphilis is not questioned in this paper. The authors only wish to bring out that the diagnosis must be substantiated by further investigation, so that the label of syphilis is not placed on an innocent victim. Needless to say, the social and psychologic implications of syphilis of childhood should cause one to stop, look and listen whenever a positive reaction to a serologic test in childhood is obtained..

ROBERTSON, Omaha.

STUDIES IN TUBERCULOSIS: III. SYMPTOMLESS TUBERCULOUS BACILLURIA AS OBSERVED IN SUBJECTS OF OSSEOUS AND PULMONARY TUBERCULOSIS. R. WEBSTER, M. J. Australia **2**:217 (Aug. 30) 1941.

Using a single cultural test, Webster found that in one group of 64 adult subjects with tuberculosis of the bones and joints 32 (50 per cent) were discharging tubercle bacilli in the urine; in another group of patients with pulmonary tuberculosis, 30 (25.6 per cent) of 117 exhibited tuberculous bacilluria. In both groups the majority of patients displayed no symptoms of urinary disorder. This condition cannot be explained by the theory of "excretory bacilluria" or "filtration bacilluria," a doctrine no longer tenable. Instead, the presence of tubercle bacilli in the urine implies tuberculous infection of the kidneys as a necessity. The lesions induced are often of microscopic dimensions, possibly no more than minute interstitial foci which make communication with adjoining tubules or ulcerative processes involving glomeruli; they excite no symptoms and lie beyond the range of clinical perception. Such clinically silent renal tuberculous damage arises commonly in persons with osseous tuberculosis and less frequently in patients in whom tuberculous disease presents itself as pulmonary tuberculosis. Fortunately many such minimal lesions heal, and only a minority progress to the stage of destruction and cavitation (renal phthisis) which demands nephrectomy.

GONCE, Madison, Wis.

INDEX OF TUBERCULARIZATION OF THE CHILD IN URUGUAY. PEDRO CANTONNET BLANCH, Bol. Inst. internac. am. de protec. a la infancia **15**:43 (July) 1941.

This study shows the urgent necessity for adopting medical, economic and legislative measures for the control of tuberculosis in Uruguay. The death rate is about 3,000 a year, and at present there are only 1,100 beds available for the care of patients with tuberculosis. This means that the isolation of the patient is totally inadequate. The author, although believing that BCG vaccination should be practiced in groups for study of its efficacy, feels that prophylaxis must depend on isolation of the diseased from the well. LESLIE, Evanston, Ill.

Diseases of Blood, Heart and Blood Vessels and Spleen

LINDAU–VON HIPPEL DISEASE: A REPORT OF FOUR CASES. WINCHELL MCK. CRAIG, HENRY P. WAGENER and JAMES W. KERNOHAN, Arch. Neurol. & Psychiat. **46**:36 (July) 1941.

Lindau–von Hippel disease consists of angiomas of the cerebellum, retina and pancreas. The disease is generally accepted as due to congenital malformation of the vascular system resulting in hemangioblastomas, most commonly in the regions mentioned but sometimes also in other places. BEVERLY, Chicago.

PHYSIOLOGICAL TACHYCARDIA IN THE YOUNG. HANS MAUTNER, ALDO LUISADA and LEO WEISZ, Arch. Pediat. **58**:562 (Sept.) 1941.

Mautner, Luisada and Weisz have made a comparative study between the heart rate, heart weight, body weight, respiratory weight and PR interval of human beings from the first day of life to the adult age. The same data were collected for animals of different species having pronounced differences in size and weight. Children were also compared with adult animals having a similar heart rate. The heart rate and the PR interval of human beings and that of various animals during their development were studied.

The general conclusions were:

1. The heart rate drops with increase in weight of the heart in growing human beings as well as in growing animals. The connection between rate and weight is shown by comparing children of different heart weight with adult animals having a similar heart weight.

2. The PR interval and the length of the ventricular systole increase with the lower heart rates. At the same time, the respiratory rate drops with a regular curve. This is true, not only in growing children but in animals of greater size, (with some few exceptions, due to species differences).

The authors believe that the volume of the heart is chiefly responsible for these changes, and therefore they do not believe that the heart rate is an exception to the general predominance of vagus excitability in childhood. ORR, Buffalo.

HENOCH'S PURPURA BASED ON FOOD ALLERGY: A REPORT OF TWO CASES. STANLEY F. HAMPTON, J. Allergy **12**:579 (Sept.) 1941.

Hampton gives a detailed report of 2 cases of Henoch's purpura. The symptoms of the disease could be produced by ingestion of various foods. Cutaneous tests for sensitivity to these foods gave negative reactions. HOYER, Cincinnati.

PROTHROMBIN: ITS ESTIMATION, CLINICAL SIGNIFICANCE AND THE TREATMENT OF HYPOPROTHROMBINAEMIA. M. TOOHEY, Irish J. M. Sc., September 1941, p. 509.

The author concludes that Quick's method, using plasma, is satisfactory as a test for prothrombin. In his own studies he uses an aqueous extract of human or

rabbit brain, which is not heated, and claims that it remains active three to four weeks if carefully stored at 4 C. He discusses the use of viper venom as a source of thrombokinase.

Prothrombin deficiencies are found in obstructive jaundice, but the jaundice must be operative three to four weeks before the prothrombin level falls; when it commences, the fall is rapid. Vitamin K in synthetic form is a potent cure for hypoprothrombinemia, particularly when given intramuscularly. Prothrombin deficiency due to actual hepatic disease will not respond to vitamin K therapy. Over 80 per cent of infants tested by the author during the first week of life had less than 75 per cent of the normal adult prothrombin content. This is greatly decreased in hemorrhage of the newborn. Toohey states that there is evidence that the incidence of intracranial hemorrhage is less in infants when vitamin K is administered to the mother prior to birth, to the child immediately after birth or to both. One patient with icterus gravis had hypoprothrombinemia which responded well to vitamin K. Stored blood shows a rapid fall in prothrombin content, losing about 40 per cent in three days. The fibrinogen content of plasma deteriorates after ten days' storage.

SNELLING, Toronto, Canada.

NUTRITIONAL ANEMIA IN INFANCY: A REVIEW OF TWO HUNDRED AND SEVENTY-SEVEN SYDNEY INFANTS AT THE AGE OF NINE MONTHS. N. C. CUNNINGHAM, M. J. Australia **2**:349 (Sept. 27) 1941.

The infants reported on had an average hemoglobin level of 11.5 Gm. per hundred cubic centimeters and an average number of red blood cells of 4,330,000 per cubic millimeter. Of the series, 7.6 per cent were suffering from nutritional anemia, a percentage which would have been much higher according to American and British standards. Infants fed with powdered milk containing extra iron were less anemic than those fed with breast milk or fresh cow's milk. Premature infants had a much lower hemoglobin level than the mean for the series; this was less pronounced in those cases in which extra iron was given in the food. The hemoglobin level of twins was only 3.9 per cent below the average for the whole series. The average hemoglobin value for the mothers was lower than the average for nurses at a local hospital. No evidence was found that the hemoglobin content of the mother's blood influenced the hemoglobin level of the infant except in 1 case. No correlation was obtained between the hemoglobin level of infants' blood and the morbidity of the infants.

GONCE, Madison, Wis.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

FOOD POISONING OUTBREAK FOLLOWING CHURCH PICNIC. HEALTH NEWS **18**:117 (July 21) 1941.

Baked beans were found to be the cause of gastroenteritis in 125 persons served at a Sunday school picnic. The beans had been obtained from a wholesale delicatessen. Staphyloccoccus albus (hemolytic) was isolated from the beans.

AIKMAN, Rochester, N. Y.

INVESTIGATION OF GASTROENTERITIS OUTBREAK PROVES PRACTICAL. Health News **18**:139 (Sept. 1) 1941.

The value of investigation of group infections is shown by this report of 12 cases of gastroenteritis that occurred after a church picnic. Infection was traced to lemonade that had been made with water from a polluted well. Steps were taken to provide a safe water supply on the picnic grounds, and no further cases occurred.

AIKMAN, Rochester, N. Y.

DIAPHRAGMATIC HERNIA OF THE STOMACH. D. S. BEILIN, Radiology **37**:68 (July) 1941.

An abnormal opening in the diaphragm results from imperfect development, anatomic weakness or trauma. Of 26 diaphragmatic hernias, only 4 were considered to be acquired. The author divided the congenital group into three types, namely: (1) complete absence of a portion or all of the diaphragm, (2) partial defect of musculature and (3) congenital enlargement of hiatuses. Relaxation of the hiatuses and trauma accounting for the acquired forms should not be confused with thoracic stomach associated with a short esophagus and eventration of the diaphragm.

Embryology.—The congenital defect of the diaphragm is due to imperfect separation of the cephalic end from the remainder of the embryonic celom by the septum transversum, complicated by subsequent growth of the liver into the caudal part of the septum transversum. Folds of the pleuroperitoneal membrane fail to separate the pleural cavities from the peritoneal cavity and complete the diaphragm. Late conditions result from growth of the lungs, separation of the diaphragm from the liver and caudal migration of the diaphragm itself. The diaphragm possesses a series of foramens and spaces for the passage of vessels, nerves and ducts. Symptoms usually result from mechanical interference with functions of the herniated viscera but are not infrequently due to interference with respiratory and circulatory organs on which they encroach. Hence they may be respiratory or gastrointestinal or both and are extremely protean. Twenty-two of the 26 patients had pain, half in the epigastric region and half elsewhere in the abdomen. Indigestion, gas or belching after eating was present in more than 50 per cent of the author's patients. Vomiting occurred in 8 cases; bleeding, in 3. One fourth of the patients had choking spells. Other symptoms were shortness of breath, weakness and loss in weight from 5 to 40 pounds (2.25 to 18 Kg.) in one year. In only 6 of the instances was the condition suspected from clinical evidence alone.

With the congenital hernias there was no elevation of the diaphragm, no paralysis and no irregularity or paradoxic excursion, in contrast to the acquired form (excluding the paraesophageal type). The lower end of the esophagus was displaced to the right in 17 patients, posteriorly in 2 and to the left in 1. Obstruction of cardiospasm was seen in 11 patients; the heart was displaced to the right in 3.

The author reports duodenal ulcer in 3 cases; diverticulitis of the esophagus in 1; diverticulum of the stomach in 1; carcinoma of the stomach in 1, and disease of the gallbladder in 1. In the majority of the cases the patient was relatively free from symptoms and the condition was discovered by routine roentgenologic examination.

ANSPACH, Chicago.

CONGENITAL PYLORIC STENOSIS. GREGORIO GOMEZ CARDENAS, Rev. mex. de pediat. **11**:118 (March) 1941.

A series of 71 cases occurring from 1914 to 1940 is reported. The first symptoms occurred with the following frequency: first week, 8.5 per cent; second week, 5.6 per cent; third week, 5.6 per cent; fourth week, 15.5 per cent; fifth week, 14.0 per cent; sixth week, 11.4 per cent; seventh week, 18.5 per cent; eighth week, 2.5 per cent and after eight weeks, 19.8 per cent.

The disease in 74.6 per cent of the cases reported was in males. Recent literature suggests that heredity may be a factor in the cause of pyloric stenosis, but this has not yet been proved.

The usual symptoms are vomiting, dehydration, loss of weight, visible peristalsis, palpable tumor and constipation. Fredet said that in order for one to feel the tumor the child must be quiet, with the abdomen relaxed, the stomach empty and

the liver not below the ribs. Under these conditions, a small olive-shaped mass may be felt below the costal margin to the right of the midline.

Medical treatment consists of feeding thick cereal, administering atropine or atropine methylnitrate (eumydrin), stomach lavage, administration of physiologic solution of sodium chloride and dextrose and transfusions. If there is no improvement, it is best to operate. The Fredet-Rammstedt operation is recommended.

GIFFEN, Toledo, Ohio.

EXPERIENCES FROM PRACTICE WITH THE SO-CALLED CATARRHAL ICTERUS AND ITS HEMATOLOGY. E. ZIEGLER, Ann. pædiat. **157**:129 (Sept.) 1941.

Epidemiologic observations of the so-called icterus catarrhalis are described, especially different cases with undoubtedly determinable periods of incubation.

The clinical picture of the preicteric stage is briefly described, and reference is made to the difficulties of differential diagnosis in just this stage.

Details are given of the analysis of the blood in the preicteric stage and in abortive forms, based on personal examinations. Further, the conditions of blood sedimentation in the preicteric and icteric stages are briefly referred to. Finally, the results of the measurement of the erythrocytes and the determination of the deformation coefficient are discussed, which in icterus, as in other damages of the tissue of the liver, have resulted in a distinct macrocythemia without deformation.

AUTHOR'S SUMMARY.

Nervous Diseases

HUMAN EQUINE ENCEPHALOMYELITIS IN KERN COUNTY, CALIFORNIA. WILLIAM C. BUSS and BEATRICE F. HOWITT, Am. J. Pub. Health **31**:935 (Sept.) 1941.

The authors report that of 316 patients admitted to the county hospital with a tentative diagnosis of neurotropic virus disease during 1938, 1939 and 1940, 116 were segregated as having equine encephalomyelitis (western type).

The seasonal incidence and epidemiologic features strongly suggested the possibility of an insect vector, particularly the mosquito. The disease ran its most typical clinical course in infants under 1 year of age, characterized by hyperpyrexia, convulsions, cyanosis, irritability, drowsiness, vomiting, muscle weakness and a residual spastic paralysis. The spinal fluid showed an increased cell count and high globulin content. The disease was much more common in children of all ages than in adults. The western type of equine encephalomyelitis virus was recovered from the brains of 2 patients who died in 1940.

Treatment consisted of administration of sedatives to control convulsions, parenteral administration of fluids and gavage feedings; small transfusions and intramuscular injections of blood, and orthopedic measures for muscular weakness. Sulfanilamide was given during the early acute phase of the disease, until purulent meningitis had been excluded.

LIMPER, Louisville, Ky.

HEMORRHAGIC ENCEPHALITIS FOLLOWING SULFARSPHENAMINE: REPORT OF TWO CASES IN CHILDREN. CLARENCE F. FRIEDMAN and MAURICE A. SHINEFELD, Am. J. Syph., Gonor. & Ven. Dis. **25**:610 (Sept.) 1941.

The basis for this article is 2 cases of hemorrhagic encephalitis following injection of sulfarsphenamine. The authors point out that this is a rather rare condition and briefly review the literature of the number of cases reported.

Two cases have been reported in detail, with the pathologic observations. The symptoms, as brought out by the presentation of these 2 patients, were: a sudden onset of headache, extreme nervousness, irritability, convulsions and finally coma. Physical examination revealed signs that are consistent with a pathologic condition of the central nervous system. In their discussion of these 2 cases the authors point out that hemorrhagic encephalitis is not always due to injections of an

arsphenamine, as cases in which it had a different cause have been reported. A brief discussion of the etiology of hemorrhagic encephalitis is undertaken, and the authors state the belief "that delayed metabolism of the arsenic due to liver insufficiency and accumulation in the body of toxic products of the drug because of kidney dysfunction seems the most likely predisposing factor." Several things can be learned from this article, namely: (1) that hemorrhagic encephalitis would frequently be prevented if strict attention were paid to the signs of arsenic intolerance; (2) that sulfarsphenamine is not as efficacious in producing cure as neoarsphenamine, and (3) that animal experiments indicate that the drug is but two and one-half times less active therapeutically than is neoarsphenamine. The authors urge discontinuance of the use of sulfarsphenamine as a therapeutic agent.

It is stated that the treatment of hemorrhagic encephalitis is highly unsatisfactory, there being a mortality rate of 79.8 per cent in the cases reviewed here. The treatment consists of administration of sedative drugs and intravenous injections of sodium thiosulfate, epinephrine hydrochloride and hypertonic dextrose solution.

ROYSTER, University, Va.

CEREBELLAR ABSCESSES OF OTITIC ORIGIN IN NINE CHILDREN. FREDERICK SCHREIBER, Ann. Surg. **114**:330 (Sept.) 1941.

The author abstracted briefly 9 cases of cerebellar abscesses in children treated surgically by him. In each instance the symptoms became manifest after mastoiditis and mastoidectomy. The principal diagnostic and localizing signs were atonia and ataxia of the arm on the same side as the abscess. Operation was delayed as long as possible without jeopardizing life from increased intracranial pressure.

BANTIN, Omaha.

MARCUS GUNN PHENOMENON: CASE REPORTS. FRANC D. INGRAHAM and JAMES B. CAMPBELL, Arch. Neurol. & Psychiat. **46**:127 (July) 1941.

A Marcus Gunn phenomenon is observed in a patient with congenital ptosis. The lid moves up with each sucking or chewing movement. It is spoken of as the jaw-winking reflex. The authors report 3 cases, the third being interesting because the phenomenon was produced by cortical stimulation.

BEVERLY, Chicago.

ACUTE POSTOPERATIVE ASEPTIC LEPTOMENINGITIS: REVIEW OF CASES AND DISCUSSION OF PATHOGENESIS. ALISTER I. FINLAYSON and WILDER PENFIELD, Arch. Neurol. & Psychiat. **46**:250 (Aug.) 1941.

Acute postoperative aseptic leptomeningitis follows 1.6 per cent of craniotomies of all kinds and 7 per cent of those with resection of the tumor. It usually appears seven to ten days after the operation and is characterized by an acute onset, with fever, stiff neck, headache, sometimes mental confusion, polymorphonuclear leukocytes in the spinal fluid and sterile cultures of the fluid. The authors suggest that it is due to a reaction from the contents of a liquefied degenerated blood clot.

BEVERLY, Chicago.

EPIDEMIC ENCEPHALITIS. RALPH S. MUCKENFUSS, Bull. New York Acad. Med. **17**:487 (July) 1941.

Muckenfuss presents a discussion of the various types of encephalitis. There has been much confusion in connection with the interpretation of the symptoms and the epidemiology of the various manifestations of this complex. In this article the author attempts to clarify the viral syndromes which constitute encephalitis.

JAHR, Omaha.

TYPICAL FAMILIAL AMAUROTIC IDIOCY IN MEXICAN CHILDREN. FRANCISCO PADRÓN, Rev. mex. de pediat. **11**:93 (March) 1941.

Four cases of this syndrome in one Jewish family are described. Of 6 children, only a girl of 10 years, who seems normal in every way, and the baby are reported living. The other 4 died at 2 months, 6 months, 8 months and 2 years of age respectively. The baby was first seen at 6 months of age. His hearing was hyperacute. He was poorly nourished and lay in any position placed when awake. A noise caused crying. Later he showed peevish, purposeless movements, easily proving muscular hypertonia, and then in a few moments laxity, not the usual action of a healthy infant when awake. At each examination, the noise and the response were the same. He was somewhat macrocephalous; the anterior fontanel was large, and the others were closed. The hair was scanty, and the veins well developed. Ophthalmoscopic examination showed normal conjunctiva and cornea, equal and regular pupils and normal occular tension. Examination of eyegrounds showed that on the temporal side of each eye there was a more or less oval white spot in the center of which there was a cherry red spot.

The cause of this disease seems connected with parents who are related.

GIFFEN, Toledo, Ohio.

Psychology and Psychiatry

PEDIATRIC TRAINING APPROACHES IN INFANCY. GUSTAVE F. WEINFELD, Am. J. Orthopsychiat. **11**:423 (July) 1941.

This is the first paper in a symposium on pediatrics and child psychiatry presented at the eighteenth annual meeting of the American Psychiatric Association. The author stresses the importance of common sense principles involved in training the child during the preschool period. The discussion revolves around modern concepts of mental development and the evolution of emotional patterns, with emphasis on existing theoretic goals and their practical limitations.

Hereditary, physical and social forces in the immediate environment and their influence on the behavior pattern of the child are given their due importance.

Of particular interest is the discussion of the present status of conscientious parents and of their effort to impose on the child all the opportunities of modern knowledge and the confusion which such parents experience in the utilization of this knowledge.

Habit training through the conditioned reflex and the factors entering into the infant's response to this technic, particularly in its refusal to yield expected reactions, is ably discussed.

This is an excellent article and could be read with profit by every pediatrician.

The prime function of the physician in this field, Weinfeld summarizes, is in the education of parents and nurses on the following points:

1. The primitive behavior of the infant depends solely on his individual intrinsic growth pattern.

2. As the infant develops, his behavior must undergo serious adaptations in order to conform to the demands of reality.

3. Adaptations are more easily made and growth proceeds more satisfactorily when the capacities of the infant are not overtaxed, his growth pattern is permitted to unfold undisturbed and his needs are fully satisfied by his immediate environment.

JAHR, Omaha.

PROBLEMS OF THE SCHOOL CHILD AS ENCOUNTERED BY THE PEDIATRICIAN. BENJAMIN SPOCK, Am. J. Orthopsychiat. **11**:430 (July) 1941.

This is the second paper in the same symposium on pediatrics and child psychiatry. It deals with a discussion of preschool and school problems encountered by the child. The author believes that pediatricians must be thoroughly familiar with

these different phases of school life if they are to render full pediatric service to the families of their patients.

The question of nursery school is an important one. What child should and what child should not attend nursery school are often important questions. Weighing advantages against disadvantages in allowing a child who is under par physically to attend nursery school is frequently a task of the pediatrician.

Fatigue in connection with schoolwork, abnormal nutritional states as they affect the child's school life, special abilities and disabilities and their effects on scholastic endeavors, all are subjects with which the pediatrician must familiarize himself.

Problems of an educational character affect seriously not only the academic but the social and emotional life of the child. Many such handicaps may be recognized early, and through timely guidance serious troubles in the later life of the subject may be averted. The pediatrician must therefore be familiar with community facilities in order to enable him to direct parents and children to sources of assistance. The pediatrician may also act as mediator between an oversensitive family and an overworked teacher in adjusting difficulties to which the child is exposed.

The conflicts of the adolescent pupils in school also receive attention. His concerns over his body, his awkwardness, his emotional instability, his pursuit of independence and self reliance and all other problems pertaining to this delicate period of life beckon the assistance of the pediatrician. It is the latter who, having followed the subject and witnessed his unfolding into a distinct personality, may be of inestimable help in the solution of problems which constantly intrude on the life of the adolescent.

Finally, the role of the pediatrician in his relation to the psychiatrist, the mutual interest which these two medical specialists possess and the parts which they play in the interpretation of the nature and the needs of the child are stressed, as are also their responsibilities for teaching medical students the art and science of management of problems of child behavior. JAHR, Omaha.

SOME TREATMENT INDICATIONS. GEORGE J. MOHR, Am. J. Orthopsychiat. **11**:438 (July) 1941.

This is the third paper in the symposium on pediatrics and child psychiatry. The author reports 2 cases as illustrating problems in treatment. One is that of a 7 year old girl who presented a feeding problem and was apprehensive, demanding and constantly clinging to her mother. The mother had to accompany the child to school and supervise her luncheon there. Her school work was poor. This child was born after twelve years of childlessness in the family. The mother had constant fear during her pregnancy, and the child was born under difficult labor followed by birth injury with impairment of vision of one eye. Her infancy was stormy. The child had an unusual amount of attention showered on her ever since birth. Her general condition, excluding the visual handicap, was good. On the psychologic scale, the patient showed average intelligence. This was a case of parental anxiety. There was much improvement after reduction of attention paid both to the mother and to the child.

The second case is that of a 6 year old girl whose complaints were vomiting, poor appetite and refusal to eat unless fed by her mother. There was a long history of struggle between the child and other members of the household, with one physician succeeding the other and obtaining no appreciable results. The child was attractive, robust and in a splendid state of nutrition. She was of high average intelligence, talkative, impudent, aggressive and demanding. She was affectionate and responsive to attention. The mother, it appears, had been frustrated in her hopes for her own achievements and was determined to make her child perfect. The mother herself had always been overprotected and had grown up in a naive, unsophisticated atmosphere. The father was an easy-going merchant, not overly competent in business affairs, who considered his wife superior to

himself in intelligence. He earned a modest livelihood for his family. He did not worry much about the child, whose management he left to his wife.

These 2 cases serve as a nucleus for the discussion of the problem of therapy, its implications and possibilities for improvement in the family. The pediatrician is logically the one on whom the responsibility falls for overhauling the family beliefs, anxieties and technics. Witnessing as he does the initial stages of these problems, he may, if he is blessed with sane judgment and proper technic for family approach, guide these confused members of the household into enlightened paths where they may rid themselves of their own conflicts before they successfully transfer these to the personality of the child.

The three papers here abstracted must be read in the original to be fully appreciated. They are followed by a discussion by Drs. Mable Huschka, Ira S. Wile, William L. Langford and Katherine Moore Wickman.

JAHR, Omaha.

GENERAL PRINCIPLES OF BEHAVIOR PROBLEMS IN CHILDREN. BERT I. BEVERLY, Illinois M. J. **80**:120 (Aug.) 1941.

The thesis of this paper may be summed up in the final sentence: Give a child security and confidence and allow him to develop habits of self reliance, and he has the best chance of normal mental growth and success in life.

BARBOUR, Peoria, Ill.

Diseases of the Genitourinary Tract

THE PRESENT STATUS OF THE GONORRHEAL VAGINITIS PROBLEM. ROBERT M. LEWIS, Am. J. Syph., Gonor. & Ven. Dis. **25**:496 (July) 1941.

In this article the author discusses briefly the change that has occurred in the treatment of gonococcic infections over the past several years. He brings out the fact that diagnosis which depends on stained spreads alone is not reliable and that cultures are imperative. He states that in a considerable portion of children the gonorrheal infection occurred in the first eighteen to twenty-four months of life. He brings out the point that in some cases of gonorrheal vaginitis in which the infection occurred at birth it takes several weeks or a month or more for this infection to become obvious, whereas gonorrheal ophthalmia in children gives rise to symptoms in from two to four days after birth. The author states definitely that the physician's desire to cure these patients sometimes leads to overtreatment, which causes more harm than good. He states that in the study in the city of New York which has recently been reported the investigators found about three fourths of all untreated control patients recovered spontaneously in twenty-eight weeks or less. The question of the contagiousness of gonorrhea is discussed, and the author reveals that toilet seats are of no importance in the spread of gonorrheal infections; he does not recommend keeping children with these infections from school until a definite cure has been established, but suggests that they be allowed to attend school as soon as their discharge has disappeared.

Under the heading of treatment the author states that the use of estrogen has been of some success insofar as the symptoms were relieved but that the cultures were positive almost as long as they were in the control group. Sulfanilamide was described as being successful in somewhere between 30 and 50 per cent of the cases. With sulfapyridine the results appeared much better, and the use of this drug was thought to be the best method of treatment at present in gonococcic vaginitis. There are reports of about 90 per cent cures. It is felt that treatment with this drug should not last over seven days and that if cure should come about with this method it should occur promptly. The author states that sulfathiazole has not been tried in this study but predicts that it will be an improvement over sulfapyridine.

ROYSTER, University, Va.

Diseases of the Muscles, Bones, Joints and Lymph Glands

CHEMOTHERAPY AS AN AID IN THE MANAGEMENT OF ACUTE OSTEOMYELITIS. GROVER C. PENBERTHY and CHARLES N. WHEELER, Ann. Surg. **114**:129 (July) 1941.

Acute osteomyelitis develops as the result of a blood-borne infection, the pyogenic bacteria entering the blood stream from some focus. The source of the infection may be the surface of the body, the upper respiratory tract or the alimentary canal. It is one of the serious diseases of childhood; first, because of the possibility of septicemia, with a fatal termination; second, because of the frequent and permanent crippling results, and third, because of the frequent long convalescence.

According to the authors, malnutrition, vitamin deficiency and trauma are possible factors in the development of the disease. From their study of a series of 19 cases of acute osteomyelitis treated with chemotherapy, the authors conclude: (1) that the mortality from septicemia can be considerably reduced by sulfapyridine or sulfathiazole therapy used in conjunction with early surgical intervention; (2) that the use of these drugs aids in limiting the amount of osseous destruction and deformity and helps, apparently, in the prevention of secondary metastatic lesions, and (3) that bone regeneration progresses more rapidly and ultimate healing occurs at an earlier date.

BANTIN, Omaha.

MELORHEOSTOSIS, WITH REPORT OF A CASE. SIDNEY V. KIBBY, Radiology **37**:62 (July) 1941.

A Japanese girl aged 5 years had a "flowing hyperostosis of a single extremity," as first described by Leri and Joanny in 1922. She experienced difficulty in walking, and there was some valgus deformity of the left knee accompanied by slight pain in the left leg which had come on gradually. There was a slight limp. Physical examination revealed nothing abnormal except genu valgum. There was no shortening of the bones or muscular atrophy.

Roentgenograms of the pelvis and lower extremity showed linear areas of increased density extending from the head of the left femur along the mesial and anterior surface of the shaft, ending in a streak a quarter of an inch (about 0.6 cm.) from the distal epiphysis. The central anterior portion of the epiphysis was involved. The patella showed spotty condensation of bone and was displaced laterally. Similar changes were present on the upper tibial epiphysis, with decalcification of adjacent osseous tissue. The tibia was rotated outward, and there was a subluxation at the knee joint. The lateral and anterior surface of the tibia was involved similarly to the femur. The astragalus was extensively involved, and slight change was seen in the os calcis, the os navicula and the first metatarsal bone. There appeared to be arrested development of the involved portion of the epiphyses, with normal growth maintained elsewhere. The literature on this subject is reviewed.

ANSPACH, Chicago.

Diseases of the Eye

ORTHOPTICS: CLINICAL EVALUATION OF RECENT ADVANCES. M. C. WHEELER, Arch. Ophth. **26**:262 (Aug.) 1941.

The author emphasizes the following points:

Orthoptic methods give valuable information about binocular function, which with further experience should prove a guide in the operative treatment.

Orthoptic training is on a much firmer footing than it was a few years ago, but its indications and limitations need further defining.

Orthoptic training should be carried out only by a qualified technician with the proper equipment under the supervision of an ophthalmologist.

Practical considerations greatly limit the application of orthoptic methods; at present, therefore, it is impractical for the average practitioner to use them routinely.

Research clinics should be encouraged to continue in as many institutions as possible, for by the building up of a large mass of data the answers to the questions presented may be reached.

WESCOTT, Chicago.

INTERSTITIAL KERATITIS: ANALYSIS OF FIVE HUNDRED AND THIRTY-TWO CASES WITH PARTICULAR REFERENCE TO STANDARDIZATION OF TREATMENT. J. V. KLAUDER and ELEANOR VANDOREN, Arch. Ophth. **26**:408 (Sept.) 1941.

This study was concerned with the evaluation of various forms of treatment in terms of visual acuity of the patients at the final examination. Vision as corrected by glasses was not always recorded, either because it was so good that refraction was not necessary or because it was so poor that glasses did not help. Ninety-seven per cent of the patients were treated with arsenicals and bismuth or mercury. Iodides, fever therapy and local heat were employed.

While treatment instituted during the inactive stage did not improve vision, routine continuous treatment with arsenicals and a heavy metal gave superior visual results; the administration of iodides unfavorably influenced final visual acuity.

WESCOTT, Chicago.

A COMPARISON OF TWO METHODS OF MEASURING DARK ADAPTATION. ROBERT E. ECKARDT and LORAND V. JOHNSON, J. Pediat. **18**:195 (Feb.) 1941.

The results of dark adaptation tests with the biophotometer and with the Hecht-Schlaer adaptometer on the same subject have been compared. It was found that the biophotometer does not use a bright enough bleach light to bleach the cones, so that cone adaptation is absent from the biophotometer curve. When the intensity of the bleach light is increased, however, the cone adaptation may be measured with the biophotometer. Within the limits of error, the rod adaptation measured with the biophotometer and that determined with the Hecht-Schlaer adaptometer are identical. The first reading obtained after the bleach period with the biophotometer is felt to represent the final cone threshold as determined with the Hecht-Schlaer instrument. Consequently, it is felt that the continued use of the biophotometer in the study of vitamin A deficiency is valid, giving a true picture of dark adaptation. It is suggested that measurements of dark adaptation be continued for fifteen or twenty minutes following the bleach period in the biophotometer test.

RAUL, Cincinnati [AUTHORS' SUMMARY].

ANGIOMATOSIS RETINAE: WITH A REPORT OF FOUR CASES IN ONE FAMILY INVOLVING SIX EYES. L. STAZ, Brit. J. Ophth. **25**:167 (April) 1941.

After a brief review of the literature Staz reports 4 cases of angiomatosis retinae in one family. A mother (aged 43), her daughter (aged 19) and her sons (aged 18 and 22, respectively) had the disease. In all, six eyes were involved. The mother, the daughter and the younger son were followed over five, one and seven years, respectively. The older son was seen but once. In none was there any sign of disease of the central nervous system or of other systems. The daughter, in whom the condition was advanced, was unsuccessfully treated by means of radium needles sutured to the exposed sclera in the region of the angioma.

The article is well illustrated.

W. ZENTMAYER [ARCH. OPHTH.].

INCORPORATION OF THE PRINCIPLES OF THE ACTIVITY SCHOOL IN THE TEACHING OF THE BLIND. GREGORIO B. PALACÍN IGLESIAS, Bol. Inst. internac. am. de protec. a la infancia **15**:23 (July) 1941.

The first American Congress for Special Training recommends that:

1. The schools for the teaching of the blind should incorporate in their technic the principles of the activity school.

2. Physical education should be accomplished by the application of sports and active games.

3. Family cooperation in the preschool education of the blind ought to be always borne in mind by the societies for welfare work and special schools, to which the development of this work should belong. With this aim, as well as for the interpretation and determination of future programs, the national welfare society should make a census of all the blind persons in the country and provide each school with the number of blind persons residing within their zone. In those countries where there is only one school for the blind, the census and subsequent work should be done by it.

EDITOR'S SUMMARY.

Skin Diseases; Allergy

GASTROINTESTINAL ALLERGY: A REVIEW OF ONE HUNDRED AND THIRTY-FOUR CASES. J. WARRICK THOMAS and CHARLES P. WOFFORD, Am. J. Digest. Dis. **8**:311 (Aug.) 1941.

This is a study of allergy in adults. It is interesting to note that cabbage was the most frequently incriminated food; milk, beans, eggs, chocolate, coffee and wheat were frequent offenders in the order named. A family history of allergy was obtained from 84 per cent of the patients.

MORRISON, Savannah, Ga.

STUDIES IN ABSORPTION OF UNDIGESTED PROTEIN: X. ABSORPTION FROM THE GALL BLADDER. MAX HARTEN, IRVING GRAY, SAUL LIVINGSTON AND MATTHEW WALZER, J. Allergy **12**:438 (July) 1941.

Previous experiments have demonstrated that the absorption phenomenon in the rhesus monkey is analogous to that occurring in human beings. In this study the authors sensitized the skin of the thigh of the animal by intracutaneous injection of a human serum containing skin-sensitizing antibodies for the antigen studied. Forty-eight hours after fixation of antibodies at the cutaneous site, the specifically related antigen was injected directly into the gallbladder. An urticarial reaction occurring at the sensitized cutaneous site marked the absorption of the unaltered antigen into the circulation. This reaction occurred in five to seven minutes.

HOYER, Cincinnati.

ORAL IMMUNIZATION FOR POISON IVY DERMATITIS. LOUIS ZISSERMAN, J. Allergy **12**:474 (July) 1941.

An enteric-coated tablet containing 0.01 mg. of an ether-soluble extract of poison ivy leaves was given to a group of 100 members of a boy scout troop. The tablets were given daily for a week and then one twice a week. The total number of tablets taken by an individual boy varied from 15 to 30. They were taken before and during the stay at camp. In 32 per cent of the 100 dermatitis developed, as compared with 36 per cent of a control group. Dermatitis developed in 52.8 per cent of the boys known to be susceptible in the experimental group and in 56.8 per cent of the known susceptible subjects in the control group.

HOYER, Cincinnati.

ASTHMA FROM INSECT EMANATIONS: REPORT OF A CASE DUE TO MOTHS. ERICH URBACH and PHILIP M. GOTTLIEB, J. Allergy **12**:485 (July) 1941.

Urbach and Gottlieb report a case of asthma found to be due to the emanations from the common or webbing clothes moth (Tineola biselliella Hummel).

HOYER, Cincinnati.

THE USE OF SULFONAMIDE DRUGS IN BRONCHIAL ASTHMA: PRELIMINARY REPORT OF TWENTY-THREE CASES. LEON UNGER, J. Allergy **12**:528 (Sept.) 1941.

Only 4 of the 23 patients reported on by Unger were improved by the use of sulfanilamide, sulfathiazole or sulfapyridine. There was no relief in the remaining

19. These were patients with intractable asthma, but their cases were not well controlled and the amount of drug used may not have been adequate, since in the few subjects for whom the blood level of the drug was determined it was found to be low.

In the discussion of the paper it seemed to be the opinion that if the asthma is on a bacterial basis treatment with a sulfonamide compound does have some value.

HOYER, Cincinnati.

ABORTION AFTER GRASS POLLEN INJECTION. NATHAN FRANCIS, J. Allergy **12**:559 (Sept.) 1941.

Francis submits a report of an abortion in a woman four months pregnant who had constitutional reactions after injection of grass pollen in the treatment of hay fever.

HOYER, Cincinnati.

A METHOD FOR THE EVALUATION OF WATER SOLUBLE AND WATER MISCIBLE FUNGICIDES USED IN THE PREVENTION OF THE SPREAD OF "ATHLETE'S FOOT." E. G. KLARMANN, V. A. SHTERNOV and S. M. COSTIGAN, J. Bact. **42**:225 (Aug.) 1941.

In their summary the authors state that this paper describes a method for the evaluation of the fungicidal action of water-soluble or water-miscible preparations, intended particularly for prophylactic purpose and for application to inanimate objects. Trichophyton rosaceum is used as the test organism. For the sake of uniformity of routine bacteriologic testing technic, the operating procedure has been patterned along the lines of the Food and Drug Administration's method of testing disinfectants.

STOESSER, Minneapolis.

ETIOLOGY AND TREATMENT OF URTICARIA: DIAGNOSIS, PREVENTION AND TREATMENT OF POISON-IVY DERMATITIS. PERRY C. BAIRD JR., New England J. Med. **224**:649 (April 10) 1941.

According to Baird, urticaria should be thought of not as a disease manifesting itself solely in the skin but as a process capable of involving many other structures and organs of the body, such as the stomach and the throat or larynx. On theoretic grounds, urticaria might extend to the lungs, producing a form of pulmonary edema; to the heart, producing paroxysmal tachycardia; to the brain, causing headaches; to the bladder, creating hematuria and then to the urethra, causing anuria.

It seems true, as indicated by Sulzberger and Goodman, that some types of urticaria are definitely not allergic. In Urbach's review of 500 cases of urticaria, he noted that only 20 per cent could be interpreted as instances of allergy. The allergic types of urticaria and angioneurotic edema are common and represent in all probability a true antigen-antibody relation in cases of pollen sensitivity, serum disease and reactions to foreign protein. It is possible that urticaria-producing drugs, such as acetylsalicylic acid, may combine with body proteins and become allergenic.

On the basis of clinical experience, it is natural to divide urticaria into acute and chronic types. The acute form usually runs a brief course, lasting from a few days to two or three weeks, and terminates as a rule in complete recovery. The chronic condition has lasted for months or years. Cutaneous tests in urticaria are of decidedly limited value.

In the search for the cause of acute urticarial recurrences, the patient's own observations regarding causative agents are of the greatest value. Frequent causes are foods, inhalants and contactants. Foci of infection represent a common cause of chronic urticaria. Nervous and emotional stress and strain can without any doubt elicit urticarial attacks. Urticaria occasionally may be caused by acrolein formed by the oxidation of fat, as in frying or broiling or in smoking cigarets

moistened with glycerin. Acrolein is related to formaldehyde, which also may cause urticaria. Many other unusual causes are reported in this article, as well as many unusual forms of treatment.

Treatment: The circulating allergens that produce acute hives are, with scarcely any doubt, usually of alimentary origin. Therefore, the first step in etiologic therapy is to clean out the gastrointestinal tract. The food should be bland and the intake limited. Fluids should be forced to aid elimination of allergens. Violent exercise should be avoided, because it increases the blood supply to the skin and increases the severity of symptoms. The relief of intolerable crises of itching is often best accomplished by application of heat, such as immersion of the part in water as hot as the skin will bear.

Poison Ivy Dermatitis.—Of all the cutaneous eruptions caused by plant substances, that produced by the different species of Rhus is probably the commonest in North America. Shelmire's experiments indicate that the dermatitis-producing principle of poison ivy is not an oil, as previously described, but a dialyzable fraction of the oleoresin soluble in water and urine.

An acute dermatitis presenting clearcut vesicles, with or without bullae, appearing suddenly on exposed regions of the body should always arouse suspicion of dermatitis venenata. Internal manifestations of poison ivy poisoning may occur. The majority of such eruptions have been caused by chewing the leaves or by swallowing the juice to obtain immunity. One of these terminated fatally (Alumbaugh).

Prophylaxis and Treatment: Protection against poison ivy dermatitis may be afforded by application of an oxidizing agent to the skin prior to deliberate exposure to the plant. Potassium permanganate solution (0.1 per cent) and ferric chloride solution (3 to 5 per cent) have been found to be useful. Also a preparation containing 10 per cent sodium perborate incorporated in a base of vanishing cream has been effective.

No type of topical application has any consistently dramatic effect in the treatment of poison ivy dermatitis. The dramatic results from therapy have seemed to come mostly from the use of poison ivy extracts given by intramuscular injection.

Topical applications of value in the treatment of poison ivy dermatitis include the following: potassium permanganate solution (0.02 per cent), boric acid solution (2 per cent), solution of aluminum acetate (Burow's solution) (diluted 1:16) and phenolized zinc oxide lotions.

Opinions regarding value of the injections for therapy and prophylaxis of poison ivy dermatitis are widely divergent. Roentgen therapy is useful and is often employed for severe and stubborn eruptions. It is effective in doses so small as to involve no hazard whatsoever.

GENGENBACH, Denver.

EXFOLIATIVE DERMATITIS (RITTER'S DISEASE) TREATED WITH SULFATHIAZOLE. ADOLPH G. DESANCTIS and F. C. DELORENZO, New York State J. Med. **41**:1361 (July 1) 1941.

A boy of Jewish parentage 16 days of age was treated for exfoliative dematitis (Ritter's disease) with sulfathiazole. Within two days marked improvement was shown. Diarrhea developed, however. This stopped when use of the drug was discontinued. The infant was discharged in ten days, having gained 10 ounces (283 Gm.) in weight.

AIKMAN, Rochester, N. Y.

THE MANAGEMENT OF INFANTILE ALLERGIC ECZEMA. GERALD M. CLINE, Wisconsin M. J. **40**:789 (Sept.) 1941.

The need for a careful history with emphasis on the possible relation of food additions to the eruption are pointed out. Since the use of superheated milks in recent years, the violent eczemas of former years are rare. In the feeding of children with allergic eczemas, if these milks do not relieve them, goats' milk or a milk substitute (soybean, etc.) may be used. Such changes have in the tests of

the author relieved about 50 per cent of his patients. When food restrictions are made, adequate vitamins and minerals, especially calcium, must be added. The dangers of anaphylactic reactions when the child is again given a previously used food are pointed out. For addition of sugar he prefers sucrose and believes that corn syrup (glucose) must be used with caution. Crystalline vitamin D_2 (calciferol), carotene and crystalline vitamin C (ascorbic acid) are substituted for ordinary forms of vitamins D, A and C. Rice is believed the least allergenic cereal. Eggs and tomatoes are most frequent offenders, while potatoes, spinach, string beans and commercially mixed greens are to be avoided.

Cutaneous testing in infantile eczema is unsatisfactory. Passive transfer testing may be helpful. Possible environmental allergens must be eliminated. Wool, feathers, glue, rubber, soap, paints, varnishes, dyes, cottonseed and kapok may be important. Scratching and traumatizing the skin must be controlled. Local applications must be individualized and varied with the progress of the patient.

JANNEY, Wauwatosa, Wis.

STUDY OF ALLERGY IN CHILDREN. MARIO SALAZAR MALLEN, Rev. mex. de pediat. **11**:274 (July) 1941.

In agreement with Piness, Barnett and Carnahan, Mallen has the impression that allergy should be considered as a nonsurgical illness; in 17 per cent of Piness' cases, tonsillectomy precipitated asthmatic symptoms; in none of the author's patients did tonsillectomy and adenoidectomy produce any improvement in the bronchial symptoms. At times the allergic child may have temporary consolidation of the lungs accompanied by eosinophilia.

The second problem is found in the cutaneous manifestation—urticaria, especially the papular form. Ratner states that the most frequent manifestation of allergy is eczema. The allergenic foods are milk, eggs, cereals, chocolate and some fruits (especially citrus fruits).

The author advises against vaccination of a baby with eczema; Asperger cites a case which terminated fatally. Allergic infants are found frequently; a review of 807 case histories gave the following figures: up to May 1941 13 per cent were allergic; of these, 66 per cent had cutaneous diseases, 32 per cent had asthma and the other 2 per cent had allergic rhinitis. One child had purpura, and others had gastrointestinal symptoms.

GIFFEN, Toledo, Ohio.

A CASE OF CONGENITAL PEMPHIGUS OF MALIGNANT TYPE. OLOF BRANDBERG, Ann. pædiat. **157**:162 (Sept.) 1941.

Brandberg gives an account of a number of known types of congenital pemphigus, especially of the type known under the name epidermolysis bullosa.

The author gives a description of a case of hereditary disease with a bullous eruption of the skin, epidermal defects and dystrophy of the nails. The disease was malignant, leading to death five days after birth. The cutaneous defects could have been provoked by mechanical lesions (Nikolsky's phenomenon). No inflammatory basis could be shown.

Epicritic discussion resulted in the placing of the disease in the group of cutaneous abnormalities known as congenital pemphigus, which at times is known under the name epidermolysis bullosa. In the author's case the fatal type was manifest.

AUTHOR'S SUMMARY.

Teeth and Dentistry

GRAFTS OF PRESERVED CARTILAGE IN RESTORATION OF FACIAL CONTOUR. CLAIRE L. STRAITH and WAYNE B. SLAUGHTER, J. A. M. A. **116**:2008 (May 3) 1941.

The authors advocate the use of preserved homografts of cartilage in plastic reconstruction. Costal cartilage obtained at autopsy preserved in merthiosaline

(a solution of 1 part aqueous merthiolate solution [1 : 1,000] to 4 parts physiologic solution of sodium chloride) may be used and reconstructive operations may be carried out, even at a young age, with grafts to suit any requirements and before psychic trauma has progressed. Ninety-four per cent of such grafts were successful.

HEERSMA, Kalamazoo, Mich.

ENDEMIC FLUOROSIS IN THE PRETORIA DISTRICT. T. OCKERSE, South African M. J. **15**:261 (July 26) 1941.

There are fifteen known sources of endemic fluorosis in the Pretoria district, and the fluorine concentrations in water in ten of these vary from from 1.43 to 13.9 parts per million. Chronic endemic dental fluorosis occurs in all these areas. In one area (Kalkheuvel) where the drinking water contains 11.78 parts per million, 8 cases of chronic fluorine intoxication were found among adults. The general clinical picture consisted in stiffness of the spine, with pain in the lumbar region and pain and stiffness around the joints of the upper and lower limbs. The roentgenogram of a patient with advanced involvement showed ossification and calcification of the lumbar and thoracic vertebrae and attachments, osteophytic growths and periosteal deposits on the radius and ulna, the elbow and the margins of the ribs.

GONCE, Madison, Wis.

Miscellaneous

OBSERVATIONS ON THE MODE OF ACTION OF SULFANILAMIDE: THE ANTIBACTERIOSTATIC ACTION OF METHIONINE. ELEANOR A. BLISS and PERRIN H. LONG, Bull. Johns Hopkins Hosp. **69**:14 (July) 1941.

The observation of Lockwood that peptone added to an unfavorable medium tended to counteract the bacteriostatic action of sulfanilamide led to the present study.

It was found that methionine in concentrations of 0.015 to 1,000 mg. per hundred cubic centimeters interferes with the bacteriostatic action of 8.6 to 17.2 mg. per hundred cubic centimeters of sulfanilamide and of smaller amounts of sulfanilamide and sulfathiazole on Escherichia coli in a synthetic medium. Arginine and lysine show this irregularly but to a lesser degree than methionine. Seven other essential amino acids and other sulfur-containing amino acids do not show this action.

LYTTLE, New York.

STUDIES ON THE CHRONIC TOXICITY OF SULFAGUANIDINE (SULFANILYLGUANIDINE). WARREN C. CORWIN, Bull. Johns Hopkins Hosp. **69**:39 (July) 1941.

This study was undertaken to determine the pharmacologic effects and pathologic changes resulting from administration of sulfaguanidine (sulfanilylguanidine) to dogs and monkeys (Macaca mulatta) for a period of one month. The drug was also administered to rabbits.

In rabbits the drug was found to be readily absorbed and excessively acetylated. The high concentrations of the conjugated drug in the blood resulted in death in 80 per cent of the animals in eight days or less. Necropsy revealed renal, splenic and hepatic lesions.

No toxic manifestations were observed in dogs receiving 1 Gm. of sulfaguanidine per kilogram of body weight daily for one month, but in 2 of 5 dogs there was moderate crystal pyelonephritis.

Neither signs of toxicity nor pathologic changes were observed in 6 monkeys receiving 0.5 Gm. of sulfaguanidine per kilogram of body weight daily in two equally divided doses for a period of one month.

In dogs and monkeys the concentration of the drug in the blood remained remarkably low throughout the experiments.

LYTTLE, New York.

THE PEDIATRIC ANAMNESIS: INACCURACIES IN ELICITING DEVELOPMENTAL DATA. MYRTLE B. MCGRAW and LOUISE B. MOLLOY, Child Development **12**:255 (Sept.) 1941.

The purpose of this investigation was to determine whether more specific questioning of mothers would elicit more accurate reports concerning the health and development of children. Mothers of 42 children on whom longitudinal developmental data had been collected were interviewed on two different occasions. In the first interview the questions were presented in a manner customary in taking clinical pediatric histories. In the second interview attention was directed to specific and qualifying details. The reports obtained during both interviews were checked against the records on file in the normal child development study. The results obtained indicate that mothers frequently failed to recall even severe illnesses. When reporting on behavior development they manifested a tendency to report dates of achievement earlier than the actual occurrence. More specific questioning not only improved the accuracy of reports but more strikingly lessened the tendency to overestimate the child's accomplishments. When questions were asked concerning the less familiar signs of development there was a tendency to underestimate the child's actual attainments. AUTHORS' SUMMARY.

USE OF SECONAL IN PEDIATRIC PROCEDURES. LAWRENCE BRESLOW and H. G. PONCHER, Illinois M. J. **80**:210 (Sept.) 1941.

The authors have found the administration of seconal (sodium propylmethylcarbinylallylbarbiturate) per rectum useful in allaying the resistance of children to certain nonpainful and somewhat painful examination and therapeutic procedures.

BARBOUR, Peoria, Ill.

REDUCTION OF DUST-BORNE BACTERIA BY OILING FLOORS. JOHN C. THOMAS, Lancet **2**:123 (Aug. 2) 1941.

The effect of spindle oil on wood floors was tested over a period of months, both in a crowded canteen and in hospital wards. In every case there was a significant and prolonged reduction (about 80 per cent) in the number of organisms projected into the air by sweeping. This applied both to the common dust saprophytes and to pathogenic streptococci. LANGMANN, New York.

SOME OBSERVATIONS ON THE EFFECT OF SEDATIVE DRUGS ON THE "CARDIAZOL" CONVULSION. N. V. YOUNGMAN, M. J. Australia **2**:224 (Aug. 30) 1941.

Youngman studied the effect of cardiazol (pentamethylenetetrazol) on guinea pigs following the administration of various sedatives. Morphine and scopolamine hydrobromide lowered the convulsant threshold, heightened and distorted the convulsive seizure and increased the mortality rate. The barbiturates raised the convulsant threshhold, lessened the activity of the various manifestations of the convulsant reaction and rendered cardiazol less toxic to the animals. The effect of cardiazol following chloral hydrate and sodium bromide was extremely variable. No experiments were conducted with paralydehyde. GONCE, Madison, Wis.

Book Reviews

Neural Mechanisms in Poliomyelitis. By Howard A. Howe and David Bodian. Price $3.50. Pp. 234, with 39 illustrations. New York: The Commonwealth Fund, 1942.

This volume is of great interest, especially to any one who has worked with poliomyelitis. It is in reality a compilation of a series of investigations by the authors, most of which have been previously published. They have to do with problems in neural anatomy and related subjects and are somewhat technical in character. Nevertheless, it is necessary for persons who are interested in poliomyelitis to understand the fundamental bases of pathology and to know the groundwork of virus behavior and how the biologic processes of the nervous system are affected by it. The authors considered neurotropism and poliomyelitis virus, the role of neurons in its dissemination, its behavior in the peripheral nerves and in non-neural tissue, the pathologic reaction, the virus-refractory state of nerve cells, the problems of immunity in poliomyelitis and second attacks. The results of their studies point to the alimentary tract as the portal of entry of the virus.

This is not a book that can be finished at one sitting. It has to be read slowly and digested as slowly, for only when it is so studied can the points raised be carefully evaluated, and only in this way can it be determined whether the authors have proved, either presumptively or conclusively, the points raised.

It has long been known that the virus of poliomyelitis has neurotrophic qualities. The evidence these authors present has strengthened the concept of neurotropism. They suggest that there may be some less well understood virus-tissue reaction which is part of a general reaction of the virus to the host as a whole. They agree with Fairbrother, Hurst and others that the virus is highly neuronotrophic, combining with the neuron itself rather than with the mesodermal glial elements of nerve tissue. They agree with others that the virus migrates along axis-cylinders rather than within the sheaths of nerves. They have roughly estimated the rate of progression of virus in peripheral nerves to be about 0.2 to 0.3 mm. per hour. They also have shown, as have others previously, that when the virus is prevented from migrating directly along peripheral nerve pathways, it may utilize a roundabout way, involving the autonomic ganglions.

They believe that the only natural route to the central nervous system in the Macacus rhesus monkeys is by way of the olfactory mucous membranes and the olfactory nerves. It might have been better said, however, that in this animal the virus can more easily approximate gray-fibered axis-cylinders in the olfactory area than it can axis-cylinders in other areas.

The authors state that although this pathway is available in the chimpanzee and in man, it is not the only natural pathway, since in some monkeys, especially chimpanzees, the central nervous system can be infected by way of the gastrointestinal tract from areas in the stomodeum or along the foregut.

In man and the chimpanzee, virus is demonstrated in the stools regularly; in cynomolgus monkeys, in the stools, walls of the pharynx, etc., liver, spleen and kidneys, etc. In the summary, it is stated that it is significant that animals in which virus is found outside the central nervous system are at the same time susceptible to virus introduced by the alimentary tract and that the M. rhesus monkeys are exceptions in that they are not susceptible to alimentary inoculations and virus is not demonstrable in their stools. The interpretation of these facts might be debatable. The authors state that the réason may be that the intestinal secretions of the M. rhesus monkey are unfavorable for survival of the virus.

They bring up the problem of host differences, potentialities for propagation in different tissues and the fact that virus exhibits varying types of behavior in different hosts.

Evidence of mutation of the organisms which may increase resistance to virus is suggested in the observation that the central nerve cells may become refractory during the time their injured axons are being reconstructed. This is an important contribution. There are a great number of theoretic possibilities as to the conditioning of the host. Diet, age and other considerations, all independent of antigenic factors, are suspected of playing a role, but none has been definitely proved to be a predisposing factor. The authors discuss the humoral mechanism.

They introduce an important concept. Certain focal areas may be protected from a subsequent introduction of virus, but other areas in the same animal are not so protected. This resistance mechanism of the tissues is unknown, although, as the authors state, it might be termed an "interference phenomenon," and they wisely set this subject aside for future discussion. They demonstrate a limited protective barrier of the pia and present conclusive evidence that the gastrointestinal tract can be a portal of entry.

The authors point out the dangers of drawing clinical conclusions on the basis of experiences with one variety of monkeys, and they mention the variables which enter the picture when many species of monkeys are used and when different strains of virus are utilized.

Although the volume presents nothing new other than what has been mentioned, it is, nevertheless, an important one because it arranges for the reader in chronologic order the investigations of the authors as well as those of others who have written on the same subject.

This book is a must for workers in this field, for any one who works with poliomyelitis virus must become a neurobiologist. Those who are interested should read the original volume. The illustrations are excellent; the logic is good, and the conclusions are sometimes understatements rather than what might have been justified by the conditions of the experiment.

On the jacket which accompanies the book, it is stated that "to those who have more than a superficial interest in poliomyelitis, the indications of these findings are of great importance. The authors have made a contribution to the knowledge of the mechanism of this disease which paves the way to a better understanding of it and to the possibility of its ultimate control." To this I subscribe.

The Dynamic State of Body Constituents. By Rudolf Schoenheimer, revised by Hans T. Clarke, David Rittenberg and Sarah Ratner. (The Edward K. Dunham Lecture for the Promotion of the Medical Sciences, 1941. Harvard University Monograph in Medicine and Public Health No. 3.) Price $1.75. Pp. 78. Cambridge, Mass.: Harvard University Press, 1942.

By the untimely death of Rudolf Schoenheimer in September 1941 biologic chemistry and the medical sciences in general lost one of their most outstanding figures, a man whose influence in the development of knowledge in these fields has been and will continue indefinitely to be deep and extensive. This monograph represents a summary of his pioneering investigations of intermediary metabolism with the important new tool the isotope. The first drafts of the lectures, to be delivered at the Harvard Medical School, were prepared by Dr. Schoenheimer. After his death the manuscript was revised and drawn up in its present easily readable and understandable form by Dr. Hans T. Clarke, of Columbia University, with the aid of Drs. D. Rittenberg and S. Ratner. The small volume affords an opportunity for both the medical investigator and the practicing physician to obtain a lucid and concise picture of one of the important new viewpoints in the fundamental field of intermediary metabolism of living things.

Only one of the many important conclusions from this work is indicated by the title of the book. The title is not meant to be taken as a general conclusion regarding body constituents. The interconversions of biologic substances are extremely numerous, much more rapid than had been previously expected but

extremely specific. Demonstration of the exact specificity of these metabolic reactions is one of the most important contributions of the isotope method, and much of the substance of the monograph is devoted to the elucidation of this specificity. The lectures deal with many intimate steps in the synthesis and interconversions of fats, proteins, creatine, urea and purines, with the subject of group transfer and with the reactions of body water. The fact of complete intermingling within the body of the molecules of a given substance, whether derived from food or from tissue metabolism, has been demonstrated conclusively by the author, and this concept replaces older ideas of separate endogenous and exogenous pathways. This common treatment of a compound by the body irrespective of its source, as explained in detail in the book, is a fact of extensive implications. The constancy of body composition in the presence of a rapid state of flux shows why investigators using older methods which relied on over-all changes in amount or relative composition often could not describe these many rapid chemical reactions.

The material is timely, important, authentic and clearly set forth. It will be read with advantage by physicians and all scientific workers in the biologic field.

The Lymphatic System. By Cecil K. Drinker, Professor of Physiology and Dean of the School of Public Health, Harvard University. Price, cloth, $2.25; paper, $1.50. Pp. 101, with 29 illustrations. Stanford University, Calif.: Stanford University Press, 1942.

Physicians who have read the recent monograph on the lymphatic system of which Dr. Drinker is co-author may profitably read these five lectures in the same field. This series of lectures is not merely an epitomized presentation of material which is found in the monograph but represents a conscientious effort to present a provocative and well documented account of the lymphatic system and its part in regulating the composition and volume of fluid in the tissues. The author's style is particularly engaging, and the material is presented in the usual lucid and scholarly manner of Dr. Drinker. The first two lectures are concerned with the evolution of the mammalian circulation and the physiologic principles exhibited in this process and the establishment and characteristics of the capillary circulation. These lectures are well illustrated and comprehensively presented. The functional aspect of this subject is stressed rather than the pure anatomic detail. The author gives the reader an excellent insight into the interplay of the lymphatic and the capillary circulation. The third lecture is concerned with the appearance and elaboration of lymphatic vessels. The historical background and functional demand of increasing complexity in mammals are discussed. The fourth lecture is devoted to a consideration of the physiology and chemistry of lymph, based on direct experiments on the mammalian heart and lungs. The intimate physiologic relation to the blood capillary system is ably documented. The final lecture is on the relations of the lymphatic system to practical problems in surgery and in medicine. These lectures could be profitably read by every practicing physician. Not only are they highly informative about a system which is generally poorly understood, but they are highly provocative of sound clinical thinking. The author's engaging style, his brevity and his faculty for dispassionate assessment of experimental fact make this collection of lectures a valuable addition to a progressive physician's library.

The Modern Attack on Tuberculosis. By Henry D. Chadwick, M.D., and Alton S. Pope, M.D. Price, $1.00. Pp. 95, with 5 illustrations. New York: The Commonwealth Fund, 1942.

One of the important considerations in judging the value of a scientific book is knowledge concerning the qualifications of its authors. Each of the authors of this small volume has had years of experience in the field of tuberculosis, and each is a recognized national authority on this disease.

The purpose of the publication is to provide a handbook on the modern methods of prevention and epidemiologic control of tuberculosis. Primarily it is intended

for health officers, public health nurses and others concerned with community tuberculosis programs. Lay members of local tuberculosis associations should also find it an excellent source of information.

The authors correctly stress the fact that tuberculosis should be regarded as one of the communicable diseases and, as such, is subject to control by appropriate epidemiologic methods. Morbidity and mortality rates with respect to age, sex, occupation, family and other contributing factors are discussed. Inadequacy of reporting the case-fatality ratio in most places is deplored. The utilization of modern diagnostic procedures for the detection of tuberculosis, particularly in the incipient stage, is described, and the role of the sanatorium in the control and treatment of the disease is evaluated. The final chapters deal with case-finding methods in the community and with organization of community campaigns for eradication of the disease.

In the reviewer's opinion this handbook, packed with factual information, should be extremely valuable, coming as it does at a time when the complete eradication of tuberculosis is in sight provided information already at hand can be put into use.

Pathology of the Oral Cavity. By Lester Richard Cahn, D.D.S. Price, $5.50. Pp. 240, with 165 illustrations. Baltimore: The Williams and Wilkins Company, 1942.

The book is essentially a textbook of clinical pathology, in which the author describes the pathologic changes and the principal clinical manifestations of "lesions of the oral cavity that are more or less commonly seen in everyday practice." The volume is generously supplied with illustrations, furnishing both gross and microscopic reproductions of most of the conditions described. To each chapter there is appended a list of references for the convenience of the reader whose interest carries him further than the relatively brief discussion of the text. The frequent reference to specific cases and the inclusion of case histories contribute to the interest and application of academic exposition.

The first chapter is particularly well constructed and gives a pertinent résumé of a modern concept of inflammation. Likewise in chapter 10 a brief description of the microscopic anatomy of the oral mucous membrane furnishes an appropriate foundation for consideration of pathologic changes in this tissue. The section of chapter 2 devoted to dental caries is less satisfactorily handled, and the statement in the discussion of caries of the crown "The process of decay usually starts in a pointlike focus and spreads fanwise toward the dentino-enamel junction" ignores the characteristic lesions that develop on the smooth surfaces of the teeth in proximal and gingival caries. The chapters dealing with endocrine disturbances and avitaminosis, though brief, are timely in the light of growing interest in these conditions.

Diseases and Injuries of the Larynx. Second Edition. By Chevalier Jackson, M.D., and Chevalier L. Jackson, M.D. Price, $8.00. Pp. 633, with 197 illustrations and 11 color plates. New York: The Macmillan Company, 1942.

This volume, the old standby, "The Larynx and Its Diseases," with an altered title and generally minor revisions, will continue to fill the place of that book, now out of print. It has the authors' usual direct and lucid style and clear and well selected illustrations, including colored plates of Dr. Chevalier Jackson's superb drawing of endoscopic images.

Because of the authors' experience and balanced judgment, their conclusions may be accepted with few questions as the best opinion in the field. The book is not designed to be read only by the special student in its field, it is so clear, informative and free from technicality that it can be read with considerable profit by other physicians, especially pediatricians. It will help solve most problems concerned with diseases of the larynx; for instance, it describes over a dozen conditions responsible for congenital stridor and tells what should be done to cure it.

This work is readable and intrinsically interesting; it will be of great value to physicians whose interests touch on the larynx.

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